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ERRATA

The editors of MEDICINE regret very much that the following errors appeared in the article entitled "The Specific Dynamic Action of Various Food Factors" by Dr. Graham Lusk, in MEDICINE, Volume I, No. 2.

Page 313, line 6: *Read* 24 *for* 14.

Page 316, line 16: (36 a) delete.

Page 318, line 5: *Read* in the first instance was deposited.

Page 318, line 25: *Read* Magnus-Levy.

Page 325, line 6, paragraph 5: *Read* must have affinities *for* must be affinities.

Page 325, last line: *Read* molecules *for* molecule.

Page 327, table, line 1, column 3: *Read* 24.98 *for* 24.81.

Page 333, line 1: *Read* When glucose.

Page 334, line 1, paragraph 4: *Read* oxidations *for* oxidation.

Page 336, line 21: *Read* less *for* more.

Page 339, legend of chart III: Should be one sentence in small caps.

Page 341, paragraph 3: *Read* whereas *for* whereas, as.

Page 342, line 17: *Read* who showed that *for* and showed that.

Page 343, table, line 5: *Read* 30 (calories per hour) *for* 70 (calories per hour).

Page 343, foot of page: *Read* COOH *for* $COOH_2$. Delete bond between formulae of serin and acetic acid.

Page 344, line 8: *Read* Jonas *for* Jones.

Page 345, line 6: *Read* See page 315.

Page 345, paragraph 4: *Read* HOOC- *for* HOO-C.

Page 347, line 13: *Read* glycollic acid *for* glycocoll acid.

Page 350, line 16: *Read* See page 342.

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THE THERAPEUTIC USE OF DIGITALIS

G. CANBY ROBINSON

Professor of Medicine, Vanderbilt University, Nashville, Tennessee

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I. INTRODUCTION

Digitalis was introduced into medicine by William Withering (163), who published at Birmingham, England, in 1785, his book entitled "An account of the foxglove and of its medicinal uses, with practical remarks on dropsy and other diseases." This book deserves a place among the medical classics, not only because it introduced digitalis into medicine, but also because it reveals an attitude of mind which should serve as a model for all who wish to bring forward any new therapeutic agent.

The words of Withering form a fitting introduction to this review. He says:

It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of

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tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies and the blindness of mankind.

Withering's views on pharmacology did not differ widely from those of today, as is indicated by the opening paragraphs of his account of foxglove.

As the more obvious and sensible properties of plants, such as color, taste and smell have but little connexion with the diseases they are adapted to cure, so their peculiar qualities have no certain dependence upon their external configuration. Their chemical examination by fire, after an immense waste of time and labour, having been found useless, is now abandoned by general assent. Possibly other modes of analysis will be found out, which may turn to better account, but we have hitherto made only a very small progress in the chemistry of animal and vegetable substances. Their virtues must therefore be learnt, either from observing the effects upon insects and quadrupeds; from analogy, deduced from already known powers of some of their congenera, or from the empirical usages and experience of the populace.

The first method has not been much attended to, and the second can only be perfected in proportion as we approach toward the discovery of a truly natural system; but the last, as far as it extends, lies within the reach of every one who is open to information, regardless of the source from whence it springs.

It was a circumstance of this kind which first fixed my attention on foxglove.

Withering indicates, at the outset, some of the various phases of study through which digitalis was destined to go. First, the empirical studies which have almost invariably marked the beginning of progress in therapeutics. Second, the study of the effects of the drug in lower animals, the period of experimental pharmacology. Third, the study of the effects of the drug on man by exact methods which allow observations approaching in accuracy those made on lower animals, the recent, present-day period. The relation of chemical structure to pharmacological action, although "abandoned by general assent" in Withering's day, represents the pharmacology of the future, which is today beginning to show far-reaching possibilities.

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As far as digitalis is concerned, however, scarcely a beginning has been made.

The literature on digitalis and its allies is very extensive, and an attempt to cover it completely has not been made. This review will include the more recent work dealing especially with the action of the drug on man, and particularly on patients suffering from heart and circulatory diseases. The literature of experimental pharmacology will be reviewed only in so far as is necessary to lead up to and explain the effects of digitalis as observed in therapeutics. There remain certain points which are better known on animals and the direct application of experimental results is necessarily made, in some instances, in the therapeutic use of digitalis. The direct application has certain difficulties which will be pointed out, and as the methods for studying the effects of the drug on patients become more and more exact, the application of experimental facts becomes less and less necessary. The relation of experimental pharmacology to the therapeutic use of digitalis will be discussed subsequently.

II. HISTORICAL DATA

Foxglove was first "noticed" according to Withering (163) by Fuchsius in 1542, who gave it the botanical name Digitalis purpurea because of the resemblance of its flowers to a finger or a thimble ("finger-hut") and because of its purple color. Fuchsius also mentioned the emetic action of the plant when eaten. Boerhaave considered foxglove a poison but Alston held that it was one of the native plants of England which should be considered a medicine of great virtue. Haller mentioned foxglove as a purge. Withering also relates the observations of Salerne, who made apparently the first experiments with the plant on animals in 1748. He fed the leaves to turkeys and described both the fatal and non-fatal effects which he observed. The emetic and purgative effects of foxglove were known before Withering's time, and the plant had been used in ointments and also as an expectorant.

Withering undertook the use of foxglove because he was informed of a secret remedy by which an old woman of Shropshire was often able to relieve and cure patients with dropsy to whom no help could be given by some of the leading medical men of the day. He obtained

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the formula which she used, consisting of some twenty herbs, and from his knowledge of medicinal plants, concluded that foxglove was the one whose action was beneficial. Withering's book was written after an experience with the drug covering a period of ten years. He gives an account of one hundred and sixty-three patients to whom he had given the drug, and also published communications from other physicians whom he had told of his early results. He states that in order to prevent any unwarranted enthusiasm for the drug, he has reported all patients to whom the drug was given without selection, and warns his readers from being led astray by the communications of other physicians from whom he had received reports of selected cases. The case reports are concise, clear and graphic but, strange to say, deal exclusively with the diuretic effects of the drug and the disappearance of dropsy. Withering observes the fact that digitalis slowed the pulse, especially when given in large doses, but he did not associate this effect with the benefit of patients suffering from heart disease. In fact it is evident that he considered the diminution of the heart rate as a sign that the maximum dose of the drug had been given, for he says: "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." This is sound advice, which for many years, has been disregarded.

The appearance of Withering's book one hundred and thirty-seven years ago represents the beginning of the period of study of digitalis by direct observations on patients, the drug being given for purely empirical reasons. The manner or method of its action were unknown and there were but few established facts on which to base hypotheses.

Cushny, Morris and Silverberg (32) have given a brief review of the varying opinions regarding digitalis following the publication by Withering. In 1799 Ferriar published "An essay on the medical properties of Digitalis purpurea or foxglove" in which he said that "the power of reducing the pulse is the true characteristic" of the drug, diuresis being a less constant and a less essential quality of the plant.

Beddoes in 1801 stated that "in a certain dose, digitalis will increase the activity of the arterial system." In this same year, Kinglake also showed that the force of the pulse was increased by the drug; and in

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1839, according to Cushny, Blake discovered that digitalis caused an elevation of blood pressure. In spite of these observations, digitalis was generally considered a cardiac sedative. Its use was advised by Pereira in 1840 in cases of pulmonary hemorrhage and aneurism. This idea was supported by Traube, who discovered that digitalis stimulated the vagus nerves during his pioneer experiments on animals in 1851, but it was abandoned after Schmiedeberg's (138) classical work published in 1874, which showed the effect of digitalis on the frog's heart. A comprehensive view of the history of the pharmacology of digitalis up to 1883 is given by Schmiedeberg (139) and will not be taken up here.

In spite of the masterly presentation of Withering, digitalis did not gain a firm foothold in medical practice until recent years. Pratt (122) has reviewed the various treatises on heart disease written by eminent English authors, in order to find out the dependence that was placed in the drug. Beginning with Allan Burns, who in 1809, published the first general treatise on heart disease, and going through Hope, Stokes, Latham and Walshe, as well as our own Austin Flint, he found that they paid little or no attention to Withering's teaching and never discovered for themselves the great value of digitalis in cardiac failure. Pratt is unable to say who deserves the credit for impressing upon the medical world the value of Withering's work. He says, however, that "Sir James Mackenzie, working over a hundred years later, was the first clinician to demonstrate conclusively the correctness of Withering's instructions regarding the administration of digitalis."

III. THE DIGITALIS GROUP

There are a number of drugs which resemble digitalis more or less closely from the point of view of their pharmacological action, which are usually included in the so-called digitalis group. They act upon the heart muscle and the musculature of arteries and stimulate certain nervous structures including the vagus centre. In this group are to be included digitalis, strophanthus, squill, apocynum, convallaria, adonis, hellebore and oleander. Abel and Macht (1) have isolated a digitalis-like body from the poison of the tropical toad, Bufo agua. They call this substance bufagin. Its marked action on the heart,

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its vaso-constrictor action and its powerfully stimulating action on the vagus centre led them to class this drug with the most effective members of the digitalis series. Many substances, of which barium may serve as an example, have a superficial resemblance in their action to digitalis, but should not be considered as members of the group. The characteristic digitalis effects are produced in experimental animals by all the drugs that belong properly in the group, the difference between them being quantitative. For this reason the various members of the group have been used more or less interchangeably in experimental work. In their use in clinical medicine, differences have been discovered, especially in dosage, rapidity and duration of action and absorption from the gastro-intestinal tract which makes their differentiation important.

As digitalis and strophanthus are by far the most important drugs of the group from the therapeutic standpoint, this review will deal with them almost exclusively.

1. Digitalis

The drug is usually derived from the leaves of Digitalis purpurea. The leaves are gathered and dried and then the drug is prepared for use by powdering the leaves or by extracting their active principles by water, alcohol or other solvents. Digitalis and its active principles have been prepared in many forms for therapeutic purposes and the best known of the preparations will be discussed when the question of the administration of the drug to man is considered.

The active principles contained in Digitalis purpurea were first studied by Schmiedeberg (138). He found that from fresh digitalis leaves, at least three active glucosides could be obtained which he called digitoxin, digitalin and digitalein. Digitoxin is the most highly active of these substances, and produces all the characteristic pharmacological effects. It is practically insoluble in water, but is easily soluble in alcohol. Roth (136) has recently given a brief review of the chemical investigations of the digitalis bodies. He says that Kiliani, who has made the most important chemical study of digitalis, gives $C_{34}H_{54}O_{11}$ as the formula for digitoxin, while the true or crystallized digitalin has the formula $C_{36}H_{56}O_{14}$. Digitalin is easily

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soluble in alcohol and very slightly soluble in water. It is found in larger quantities in the seeds than in the leaves of digitalis.

The term "digitalin" has been used to denote a variety of preparations which has served to bring into the literature considerable confusion. Hatcher and Eggleston (78) state that the name is meaningless without a qualifying term, and it has been used to mean digitoxin, true digitalin, or a mixture of the latter with digitonin, a saponin-like substance. Other instances of such confusion are found in the literature dealing with the digitalis group. This is much to be regretted and careful consideration should be given to this question of terms. A general agreement in this connection is much desired.

Digitalein is a water-soluble glucoside which Schmiedeberg considered a pure substance, while Kiliani looked upon it as a mixture.

Besides the active substances that have been mentioned, digitalis also contains a saponin-like body called digitonin. It is inert as regards the characteristic digitalis effects, but according to Roth (136), it is due to the digitonin that aqueous solutions of digitalis leaves contain the water-insoluble substances, digitalin and digitoxin.

As stated by Roth, Kraft in 1912 isolated from a watery extract a glucoside which he named "gitalin" which he considered a purified digitalein. Both Kiliani and Rosenthaler worked with gitalin in 1914, and concluded independently that it was not a definite substance and could be resolved into constituents having unlike chemical and pharmacological properties. Several other investigators have attempted to shed further light on the chemical constituents of digitalis and in 1913 Kolipinski isolated an acid resin which he named "digitalic acid." He concluded from his many animal experiments that "digitalic acid" possessed all the virtues, without any of the poisonous properties of digitalis when used in therapeutic or larger doses. He also considered that it produced no cumulative effects and was not irritating when used subcutaneously. The work of Kolipinski would have held promises of definite advance in the therapeutic use of digitalis, if it had been confirmed by further study, but the investigations of Sharp and of Smith in 1914, failed to substantiate Kolipinski's claims, as both reached the conclusion that digitalic acid has no pharmacological effects whatever, being an inert substance.

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2. Sources of digitalis

For many years, the English-grown leaf, especially those marketed by Allan, was considered the standard source. During recent years, however, the greater part of the supply of digitalis used in the United States came, according to Roth (135), from Germany and Austria. When this source of supply was cut off during the years following 1914, by the turmoil of war, attention in the United States was turned to the home-grown product. Wilbert pointed out that Digitalis purpurea grew abundantly in California, Oregon and Washington and, to some extent, in West Virginia. In these states, it is found growing wild, and is considered a "weed" in various parts of the country. American leaves were used by Rowntree and Macht (137) in 1916, who prepared infusions from them as well as from European leaves, and when the pharmacological activity of these infusions was determined on cats they found that the highest potency was possessed by the infusions of American leaves.

Roth (135) investigated the activity of wild American digitalis in 1917 using leaves gathered in the States of Oregon and Washington. The leaves were air-dried and tinctures were made of them, the assays being conducted by the one-hour frog method. He found that the wild digitalis from the Northwestern States was of sufficient strength to allow its use as a source of supply in making the various official preparations of digitalis, and he concluded that by the use of ordinary methods in handling and preparing the leaves, a highly active product could be secured which compared favorably with the activity of cultivated leaves grown under more favorable conditions.

A new species of the American-grown plant, Digitalis lutea, has recently been employed and its efficiency tested on both animals and patients. White and Morris (139) have used this form of digitalis grown in Minnesota, and have compared its activity with Digitalis purpurea. They find that Digitalis lutea possesses the same therapeutic value as purpurea and seems to have less effect on the gastro-intestinal tract. Christian (16) reports that he has had excellent clinical results with American-grown digitalis, and Pratt (122) who has used both American-grown purpurea and lutea, says that active leaves grow in various parts of the United States from Maine to the Pacific Coast.

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Pratt and Morrison (123) tested out twenty-five samples of American grown digitalis by the one-hour frog method, using both purpurea and lutea. Their work shows that the best American digitalis, both wild and cultivated, is equal in activity to the best European digitalis. They obtained specimens of high potency from Virginia, Nebraska, Wisconsin, Minnesota, Oregon and Washington. There was, however, a definite difference in the potency of various samples, and seventeen out of twenty-five were below the standard of strength required by the United States Pharmacopeia. The average strength of the American-grown leaves was greater than that of the various imported leaves examined. Pratt and Morrison suggest that samples from a crop of digitalis should be tested biologically before it is gathered in large quantities for therapeutic use.

It may be considered as established that digitalis of good potency grows in America in both the wild and cultivated state so that dependence need no longer be placed upon the European market. The species Digitalis lutea seems also at least as useful as the Digitalis purpurea, and may prove to have some advantages over the better known species.

3. Strophanthus

This drug was introduced into medicine by Sir Thomas Fraser (55), who discovered it during an investigation of the arrow poisons used by certain African tribes. Several variations of the plant Strophanthus Kombé, S. hispidus, S. Gratus, and others contain the active principle of the drug, the seeds being especially rich in it, and are used in making the various preparations for therapeutic use. Hatcher and Eggleston (78) have pointed out the uncertainty of origin of much of the strophanthus of commerce, and state that they are not convinced that all commercial specimens of strophanthus—even those obtained from reputable dealers—are sold under their correct botanical names. This is perhaps more of an academic question than one of importance from the point of view of therapeutics, as the active principle, strophanthin, appears to be identical in its pharmacological properties, regardless of its source. Hatcher and Eggleston state that the active principle, strophanthin, has also been considerably confused. The term is properly employed only as

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applied to amorphous strophanthin, but it has also been used for ouabain and "crystalline strophanthin-g." Ouabain is a crystalline substance obtained from strophanthus and represents the purest chemical substance, possessing the most potent activity of any body belonging to the digitalis group. It was isolated in 1888 from ouabain wood by Arnaud, who gave it its name and established its identity with that of the active substance obtained from Strophanthus gratus. This same substance was called by Thoms sixteen years later "crystallized strophanthus-g." As amorphous strophanthin and crystalline strophanthin or ouabain are both used therapeutically and may differ much in potency, this confusion of names is very unfortunate and should be avoided.

Strophanthus and its active principle possess all the pharmacological properties of digitalis, and the solubility and potency of strophanthin and ouabain make them important members of the digitalis group, being especially valuable for intravenous administration.

4. Other members of the group

Other members of the digitalis group have not a well established place in therapeutics, although some of them have been extensively used. Recently the action on man of several members of the group have been studied by modern methods by White and his collaborators. Squills, apocynum and convallaria have been administered to patients in whom the action of these drugs was compared with that of digitalis. These studies will be referred to when preparations are considered, but it may be stated at this time that they showed several reasons why these drugs are not as suitable, not as efficient as digitalis, and that they should not be used in the treatment of heart disease. Less is known about other members of the group. For these reasons the discussion of their action and their therapeutic use will not be included in this review.

IV. THE POTENCY OF THE DIGITALIS BODIES

1. The biological assay

The determination of the potency of a drug by quantitative chemical analysis is seldom feasible when the activity of the drug depends upon the presence of one and often of several chemically complex substances.

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This has proved especially true of members of the digitalis group to which biological or pharmacological assays have long been applied. According to Hamilton (65) the earliest recorded attempt to standardize digitalis bodies by means of their effects when injected into animals was that of Fagge and Stevenson in 1866. The drug is administered to an animal in such a way that the amount necessary to produce a clearly defined and constantly occurring phenomenon can be accurately measured. By this method of assay the potency of various members of the digitalis group can be compared, and the various preparations for therapeutic use can be standardized.

A number of methods for the biological standardization of digitalis have been employed. Generally speaking, they depend on the determination of the minimal amount of drug required to kill the animal used. This method has been objected to as inapplicable to therapeutics as physicians do not want to kill their patients but to cure them. Hatcher (67) has made the following reply to this criticism:

> While it is perfectly true that physicians do not wish to kill their patients, it is equally true that the action of digitalis which they utilize in curing them is that which kills if it be carried too far, and it seems to me that it would be quite as logical to object to testing the strength of strands of cable by raising the tension to the breaking point, on the ground that engineers wish the cable not to break, as it is to object to the method in vogue for testing the activity of the digitalis bodies on the grounds mentioned.

There seems to be no better method of standardizing the digitalis bodies than that which depends on their power to kill.

The animals most commonly used for biological assays of digitalis bodies are the frog, the cat and the guinea pig, although the dog and the rabbit have been used by some experimenters, and one method has been suggested which depends on the determination of the minimal lethal dose for gold fish. The original method used by Fogge and Stevenson depended, according to Hamilton (65) upon the time required for the systolic stoppage of the exposed heart of the frog, after the drug was injected subcutaneously into the thighs. This general principle has been widely applied, and it has been recently especially elaborated and advocated by Focke (53). The frog test as employed

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in 1916 (Roth, 136) by the Hygiene Laboratory of the United States Public Health Service, aims to determine the quantity of digitalis which will produce permanent systole of the ventricle, in an hour, when injected into the ventral lymph sac. Certain conditions, such as temperature at which the tests are carried on, the concentration of the injected fluid and its alcohol content, are kept constant. Roth states that a very disturbing factor in the one-hour frog method is that of absorption. The assay of digitalis by the frog method has been used with a number of modifications. In determining the minimal dose causing permanent systolic stoppage, the heart is necessarily exposed after the frog has been pithed, while in determining the minimal lethal dose this is not done. Hamilton (65) who has recently reviewed all the various methods of biological assay of digitalis that have been employed, apparently prefers the frog method and considers that there are advantages in determining the minimal lethal dose, namely, that less work and time are involved, that the factor of slow absorption is eliminated and that the end-point of the test is not obscured by rough handling necessitated by the pithing and laying bare of the frog's heart. However, in testing digitalis, it is not the general toxicity as much as the potency of the drug on the heart itself that is the essential feature, and therefore the systolic stoppage method with the heart exposed should be considered that giving the more exact information.

Hatcher and Brody (74) in 1910 proposed their cat method of standardization. This method determines the minimal lethal dose per kilogram of cat when the drug is injected slowly into the femoral vein. This amount, these authors have termed "the cat unit." For crystalline ouabain, the cat unit has been found to be 0.1 mgm., this amount of the drug per kilogram of cat being fairly constantly fatal when injected during a period of about ninety minutes. In testing other digitalis bodies Hatcher and Brody found that the accuracy could be increased by the following procedure. A measured amount of the digitalis body (tincture or infusion of digitalis, or digitoxin) is injected into the femoral vein in the first period of about ten minutes and after an interval of twenty minutes, the injection is resumed but a solution of crystalline ouabain is substituted for that of the digitalis body. This injection is continued slowly until the death of

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the animal occurs. The difference between the amount of crystalline ouabain actually used to complete the assay and 0.1 mgm. per kilogram of animal (the amount which would have been required in the absence of the digitalis body) represents the activity of the digitalis used. There are certain precautions which the authors state, especially regarding the selection of animals, which should be followed. This method was adopted after the authors had assured themselves that ouabain was capable of replacing the other digitalis bodies.

The cat method is given in detail because of its increasing popularity especially with those administering digitalis accurately and carefully to patients. It is suitable for the standardization of the generally used therapeutic preparations, such as the tincture of digitalis, and can be carried out in any properly equipped laboratory, but its use by the retail pharmacist, as suggested by the authors, seems to the writer, to be, generally speaking, somewhat idealistic although highly desirable. The method has been criticized by Eckler (35) as complicated, time-consuming and expensive, and he points out a number of unknown factors that are involved, but he concedes that it has one point of superiority over all other methods in that the matter of absorption is entirely eliminated.

Macht and Colson (105) express as their opinion that the "cat method" gives more uniform results than the frog method, but they found that the fatal dose varies considerably in cats. They conducted two series of experiments: one in which the vagi were cut while the nerves were left intact in the other. Using digitalis, digitalin and strophanthin, they found that the results were more uniform in the series in which the vagi had been cut, but that the drugs were more toxic for these animals.

Hamilton (65) states that "the cat method is purely a toxicity test and can be classed with that on guinea pigs as objectionable because death is almost invariably due to paralysis of the respiratory center and therefore, not directly a measure of the heart toxic value." The experience of the writer with this method is not in accord with this statement. Respiratory changes practically always occur after the heart has ceased to beat, as revealed by the electrocardiograph. Auscultation of the cat's heart is also a helpful method of determining the end-point of the experiment, when digitalis is being injected intravenously.

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Eggleston (41) has published a criticism of the cat method of Hatcher and has compared it with the twelve-hour frog method of Houghton, the one-hour frog method of Famuleuer and Lyons, and the guinea pig method of Reed and Vanderkleed. He discusses in detail the various factors which he considers important in the choice of a method for the biological standardization of the digitalis bodies. Eggleston concludes that there is no perfect or ideal method, but that each of the four methods discussed has certain advantages not possessed by the others. He considers, however, that the cat method of Hatcher possesses the greatest number of advantages which are as follows:

(*a*) It is accurate to within 10 per cent. (*b*) It gives constant results from year to year. (*c*) It provides a means of detecting the presence of deterioration. (*d*) It is the least affected by adventitious factors. (*e*) It tests the action of the drug upon which its therapeutic use depends. (*f*) It is not too difficult for general use. (*g*) It is neither time-consuming nor too costly. (*h*) By it, widely different preparations can be compared accurately. (*i*) Its results are transferable to man. (*j*) It has the widest range of applicability of all the methods.

Neither the frog nor the guinea pig method fulfils so many of the essential requirements as does the cat method. The cat method fails in no single requisite and has far fewer disadvantages than any other method yet proposed.

Another advantage which the cat method of standardization seems to the writer to possess over the frog method may perhaps be described as psychologic. It is easier to think of dosage in terms of cat units than it is in terms of frog units. Hatcher and Brody quote Focke as saying that he believes it is not feasible to accustom physicians to thinking and calculating the strength of digitalis preparations in frog units. On the other hand, the cat unit strength of the various forms of digitalis is becoming widely accepted. The figures are larger and therefore more nearly approach the therapeutic doses, and they also tend to fall into certain multiples which make them readily applicable for calculations of dosage. Eggleston is of the opinion that the relative toxicity of the various digitalis bodies for the cat corresponds more accurately to the relative potency of these drugs for man than does their toxicity for the frog or guinea pig.

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It is very desirable that all forms of digitalis should be biologically assayed by a uniform method, preferably by the cat method for reasons that have been given. The strength of every preparation put upon the market should be indicated preferably in terms of the cat unit, and the date of manufacture and of assay should be stated. In the case of some preparations, and probably in many, the strength of the drug can be adjusted so that a fixed amount has a constant strength. For example, 1 cc. of the tincture should always represent 1 cat unit no matter by whom it is manufactured. This adjustment of strength is very desirable. When this becomes a uniform procedure, the medical profession will learn to use the preparations of digitalis according to their individual potency, and not follow a rule of dosage which may have but little bearing on the preparation being used.

Even though the strength of a preparation of digitalis, as determined by the biological assay method is known, the physician should always study the relation between the amount of the drug given to patients and its effect upon them. He should endeavor to determine the average amount of every preparation that is used necessary to produce well defined digitalis effects. If opportunities are afforded for doing this adequately, as can be obtained in modern hospital practice, perhaps the best method of digitalis standardization for practical purposes is available.

2. The relative potency of the digitalis bodies

The potency of a number of the more important members of the digitalis bodies was determined by Hatcher and Brody (74) and later Hatcher (68) repeated some of this work, correcting a few of the figures reported with Brody. From these two papers the relative potency of these drugs may be tabulated, the number of milligrams of the drug which represents 1 cat unit, or the number of milligrams which is the fatal dose for the cat on the basis of 1 kilogram of body weight of the animal, being used to express their potency.

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	mgm.
Ouabain, crystalline	0.10
Strophanthin, amorphous, Boehringer and Sons	0.13
Merck	0.17
Digitoxin, crystalline	0.30 – 0.50
Digitoxin, so called amorphous	1.20
Digitalinum verum, Kiliani	1.50
Adonidin	3.00
Strophanthus, Kombé	3.00
Digitalein	3.50
Digitalin, German	3.60
Digitalis, German	82.00
Digitalis, English	92.00

This table indicates clearly the relative potency of the three active principles of digitalis, digitoxin, digitalin and digitalein, and shows also the relative toxicity of ouabain and amorphous strophanthin.

3. Variations in potency

The varying strength of the preparation of digitalis has been a problem which has caused much uncertainty and discussion. It has confused the question of dosage. The chief sources of the difficulty have been variations in the digitalis content of different specimens of leaves, deterioration and probably variations in absorbability from the gastrointestinal tract. Roth (136) found that in 1916 the methods of biological standardization employed by American drug manufacturers were not uniform and, in some instances, manufacturers were not carrying out a biological standardization of their digitalis products.

Pratt (121) was among the first to show the inefficiency of some of the digitalis on the market. By using the thirty-minute frog method he assayed nine samples of digitalis leaf obtained from leading apothecaries and hospitals in and about Boston, and found only one strong digitalis leaf among the number. A sample obtained from Germany prepared and standardized by Caesar and Loretz proved to be twice as strong as the best leaf obtainable in the American market. Pratt concluded that the available tinctures were also low in potency, as he was unable to obtain the therapeutic results with them which were immediately obtained in the same patients when good powdered leaves were used. Goodall, according to Fulton (56), examined a number of tinctures of digitalis over a period of three years and found

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that during this time, nearly half the number had departed from the standard strength, the limit of variation being from 275 per cent over-strength to 40 per cent under-strength. Goodall found that the tincture was apt to deteriorate within a year. The writer found that one lot of the tincture kept in the drug room of a hospital in a 5-gallon container, and which had a cat unit of 1 cc. when first tested, had deteriorated so that the cat unit was approximately 2 cc. at the end of one year.

Roth (136) found by the one-hour frog method a variation of over 250 per cent in the thirteen samples of commercial "fat-free" tincture of digitalis and a variation of 150 per cent in five samples of German commercial digitalis. No definite reason could be given for the initial variations in the samples of the fat-free digitalis.

Newcomb and Rogers (115) who also found differences in the strength of various preparations, consider that the chilling of the tincture of digitalis to a temperature of 40°F., even for a brief period of time, causes an increase in the natural precipitation, which carries down some of the active principles of the drug.

On account of the opinion prevalent among physicians and pharmacists that digitalis and its preparations undergo deterioration with considerable rapidity, Hatcher and Eggleston (76) reviewed this subject and undertook an investigation on the keeping properties of digitalis and some of its preparations. The cat method and, in some instances, the one-hour frog method were employed for estimating the activity of the specimens. They used samples of leaves, ground and unground, tinctures, extracts and fluid extracts ranging from less than one to more than thirty years old. Their findings do not confirm the common belief regarding deterioration, as they found that commercial digitalis leaves of good quality do not undergo any deterioration in many instances as the result of age. In a few cases they do appear to have deteriorated but only with extreme slowness—at a rate probably not exceeding 1.5 to 2 per cent a year. Although the presence of moisture has been emphasized as a cause of deterioration, several of their specimens of leaves had not been protected from moisture. Mouldy leaves, however, must be considered as worthless. Pharmacopial preparations made with a menstruum containing at least 50 per cent alcohol showed no greater deterioration than the

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leaves. Of course, the infusion of digitalis is notoriously unstable and those using it carefully usually insist on its preparation within a few days of its administration. Hatcher and Eggleston (77) studied the stability of the infusion, using the same methods employed in their previous work. The most striking facts shown by their experiments are that an infusion of digitalis made without alcohol and kept without the least care, in fact under more unfavorable conditions than should obtain in practice, may retain its activity with little impairment for periods varying from six to nineteen days; and that when the hot infusion is bottled with reasonable care, it will often keep practically unchanged for many weeks even during the summer.

The stability and constancy of the purer substances, such as the single glucosides and especially the crystalline substance such as ouabain would be expected to render them above reproach, from the point of view of stability. But such is not the case. Sollman (142) has pointed out several factors, especially variations in temperature and concentration of the solution which affect the toxic dose of ouabain in frogs, and which may cause errors in the biological assay of the drug. Deterioration of crystalline strophanthin has been found by Levy and Cullen (95) in the preparations marketed for therapeutic purposes. They studied the cause of this deterioration and propose a well founded remedy for it. Many of the glass containers commonly used in the laboratory and most of the glass ampules employed in marketing sterile solutions for hypodermic or intravenous medication yield sufficient alkali on autoclaving to change the reaction of distilled water from pH 6 to pH 9. This increase in alkalinity is sufficient to render biologically inert and practically to decompose aqueous solutions of crystalline strophanthin in the concentration employed in clinical medicine. Levy and Cullen suggest that for clinical use crystalline strophanthin be dissolved in 0.02 M standard phosphate solution at pH 7 and marketed in hard glass ampules, thereby insuring stability of reaction and preservation of the biologic activity of the drug. This work views the question of deterioration of the digitalis bodies from a new angle, from which the deterioration of some of other members of the group should be studied.

The relative potency of the tincture of squill when administered orally as compared with the tincture of digitalis is shown by the recent

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work of White, Balboni and Viko (158). They investigated the effect of a standardized tincture of squill on the hearts of a series of patients and found that although squill has a definite digitalis-like action on the heart, it appeared only after doses eight to sixteen times as large as those generally recommended. These observations confirm the opinion of Cushny (30) that, considered clinically, squill has only one-half or one-quarter the effect of digitalis.

The question of absorption from the gastro-intestinal tract is one that complicates the problem of the effects which the various digitalis bodies exert when administered by mouth. As it is not primarily a matter of the relative potency of the various members of the group, it is best discussed after the question of dosage has been taken up.

V. ANIMAL EXPERIMENTATION

The effects of digitalis and its allies on animals have been studied by many investigators and there is an extensive literature on the subject. Those studies in which mammals have been used have furnished the more valuable results from the therapeutic point of view, and some of these studies will be reviewed. These experiments have served as a basis for the analysis of the effects observed in man during the so-called empirical period of the use of digitalis, and they have also pointed the way to the improvement in methods of administration. They have been of great value in rationalizing the therapeutic use of the drug, so that today a fair degree of scientific accuracy is possible in regard to its use. On the other hand, animal experimentation has too strongly dominated the ideas concerning the results to be expected when the drug is administered to patients with heart or circulatory disease.

As Cohn (20) has pointed out, Schmiedeberg and his pupils have emphasized, that the main action of a digitalis body is on the heart muscle; while the school of Gottlieb has been particularly interested in the effects the drug has on the blood vessels, and maintains that it has an important action on the walls of the arteries. "Both schools find that the drug increases the excursion of the heart in contraction, both believe that it elevates blood pressure, both believe that it increases the amount of renal secretion." Recent observations on patients by methods which allow an accuracy closely approaching

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that of animal experimentation, make it necessary to readjust our ideas, as the predominating effects on patients on which the beneficial results of the drug depend are not those predicted by animal experiments. The careful clinical observations of Cohn have been of importance in bringing out this point, and he says:

> It is perhaps not an overstatement to say that in a general way clinicians have been too much influenced by these experimental results and have felt obliged to find that the administration of the drug in patients results in parallel phenomena. It requires a very small experience in treating patients suffering from heart disease to find one's self disappointed because the expected results did not occur. And when discrepancies were noticed, the discovery was not often followed by an effort to explain them, the subject was often dismissed by finding fault with the potency of the drug or by discovering an idiosyncrasy in the patient. But even if drugs were always potent and there were no individual idiosyncrasies, it is extremely likely that patients would continue to react in different manners to the drug. And the reason for that must be that individuals, although they suffer from what, in a general sense, is called heart disease, yet present a great variety of clinical pictures.
>
> There can be no question of the usefulness to therapeutics of these experiments; as guides, they are indispensable, but it must be clear that they neither replace nor parallel the clinical conditions we must treat. That there has consequently been a divergence between the results of the pharmacologists and clinicians in a practical sense is inevitable. The responsibility for it is probably shared equally by both. Pharmacologists have dealt usually with simple normal conditions; clinicians with complex pathologic ones.

This review attempts to emphasize the recent careful studies of the effects of digitalis on patients and gives preference to the work from the clinic over that from the laboratory, when the clinical studies are such as to justify this preference. The more exact clinical studies of digitalis were inaugurated by Mackenzie (107) and he was perhaps the first to point out in 1911 that the clinician must exercise great judgment in the application of pharmacological knowledge in the treatment of his patient. The confusion of results from the laboratory and of those from the clinic is caused mainly by the fact that observations have been made on widely different species and that great differ-

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ences in dosage have been employed. Uniform criteria have not been employed, and the tissues on which the drug acts have not been exactly ascertained.

The most important statement regarding the question of the value of animal experiments on the therapeutic use of digitalis is that made in 1918 by Cushny (31) one of the foremost experimentalists with digitalis. He said:

> More than a century after the introduction of digitalis, the knowledge of its therapeutic action had made but little progress and was meagre and unsatisfactory, because no accurate knowledge of the clinical action was attainable, and the facts of the laboratory could not be confirmed for man.

Cushny who studied patients with Mackenzie has done much to introduce the new chapter in the study of digitalis, the chapter of exact clinical observations. In his important experimental work, published in 1897, he employed a method which was a forerunner of one of the clinical methods that have thrown much light on the problem of digitalis action. Cushny (28) studied the action of the drug directly on the heart of the dog and observed, by means of the myograph the action of the auricles and ventricles separately, thus making it possible to differentiate the various forms of disturbed cardiac mechanism which have become so important in the clinical study of the drug.

VI. THE NEWER METHODS OF CLINICAL STUDY OF DIGITALIS

The newer methods may be put into two groups. In the first group belong those methods that give accurate information regarding the movements of the various parts of the heart. In the second group, may be put the quantitative clinical methods such as the accurate measurement of the intake and output of fluids, the quantitative estimation of kidney function, the measurement of blood pressure and of the vital capacity of the lungs, together with the variety of useful procedures that have been developed by the application of biochemistry to clinical medicine. All of these methods have been used, not only directly in the study of digitalis in man, but they have also served to differentiate with greatly increased accuracy the many conditions belonging to the general class of heart and circulatory disease, and have so added a degree of specificity to digitalis studies which was hitherto impossible.

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The introduction of the polygraph by James Mackenzie inaugurated the methods by which the movements of the auricles and ventricles of man can be studied separately, and by which the efficiency of the mechanism conducting the cardiac impulse from one chamber of the heart to the other can be determined. The value of this method is demonstrated by the masterly studies of digitalis published by Mackenzie (106, 109) in 1905 and 1911 which have added much to our knowledge of the action of the drug in heart disease.

The adaptation of the string galvanometer by Einthoven furnished the second great advance in this direction, and the electrocardiograph has added much to the modern concepts of digitalis action in man. In it we possess a method that not only clearly differentiates all the disturbances of cardiac mechanism, but which also gives us information of importance regarding the direct action of digitalis on the heart muscle, allows the detection of very early toxic effects of the drug on the heart, and serves as an aid in determining pathological conditions of the myocardium.

Although these two methods are not perhaps as yet available to all practicing physicians, the information which they yield is translatable, as Christian (14) remarks "into the terms of general practice, that is, brought into the range of such observations as is possible with fingers, eye and stethoscope."

Of the methods belonging to the second group, comment is necessary perhaps in only one instance, namely the measurement of the vital capacity of the lungs as a means of studying the effect of digitalis. Several years ago, Peabody showed that the vital capacity of the lungs (the amount of air, measured by a spirometer which can be forced from the lungs after the deepest possible inspiration), varied directly with the efficiency of the circulation. He also showed that normal individuals of the same sex, weight and height gave vital capacity readings of sufficient constancy to allow the establishment of a normal standard. West and Pratt (156) have recently reported a series of cases to which digitalis was administered and in which the vital capacity of the lungs was taken as one of the criteria for the estimation of the effect of the drug. Although it is not entirely clear how the improvement of the circulation causes an increase in the vital capacity, the method holds promise as a means of estimating quantita-

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tively the functional efficiency of the circulation, and may therefore fulfill, at least in part, one of the greatest needs in the study of the effect of digitalis in heart disease. This method, the technique of which is quite simple, should be included in all comprehensive studies of the effects of digitalis on man.

VII. THE TOXIC EFFECTS OF DIGITALIS

In considering the effects of digitalis on man, they are naturally separated into those that are advantageous and those that are deleterious, especially to patients suffering from heart and circulatory disturbances. These two groups of effects may be spoken of as the therapeutic and the toxic effects. In most instances, the two groups can be separated by the ultimate results of each on the circulation as a whole, but sometimes the prevailing conditions of the circulation may make this separation somewhat difficult, as effects which would be considered toxic, under most circumstances, may have, under some conditions, therapeutic value. Therapeutic and toxic effects may also occur simultaneously when the drug is being administered in large doses to patients, and the close relation between the optimum therapeutic dose and that producing early toxic symptoms presents one of the greatest problems involved in the skilful use of the drug in therapeutics. For instance, Bailey (quoted by Bastedo (5)) found that of ninety patients in Bellevue Hospital taking digitalis, about 25 per cent showed one or more toxic effects of the drug.

The characteristic effects of all members of the digitalis group are those on the heart and on the central nervous system, but in order to understand the action of these drugs so that they may be intelligently employed in the treatment of disease, a close analysis of their effects must be made and careful consideration must be given to the various pathological conditions they may be expected to benefit.

The first requisite for the successful employment of digitalis as a remedy is the recognition of its toxic effect, especially of those early effects which serve as indications for the discontinuance of the drug. For this reason the deleterious or toxic effects of the drug will first be discussed.

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1. Gastric effects

In the earliest accounts of digitalis, reviewed by Withering (163), the effects of the drug on the gastro-intestinal tract were described, and it was spoken of as a poison having an emetic and a purgative action. All modern study of digitalis has taken into account the gastric symptoms, loss of appetite, nausea and vomiting which constantly follow the use of all members of the digitalis group in large doses; and they have been recognized as among the earliest toxic symptoms which the drug produces.

Anorexia, nausea and vomiting are symptoms observed by all who have used digitalis in sufficient doses, as they are probably the commonest of the "side-actions" as Eggleston puts it, encountered in the clinical use of the digitalis bodies.

The peculiarities of the emetic action of digitalis were noted by Withering (163) who wrote:

> It is curious to observe that the sickness, with a certain dose of this medicine, does not take place for many hours after its exhibition has been discontinued. . . . . The sickness then excited is extremely different from that excited by any other medicine; it is peculiarly distressing to the patient; it ceases, it recurs again as violent as before; and then it will continue to recur three or four days at distant and more distant intervals.

Vomiting should be avoided if possible, especially when digitalis is being given to patients with severe symptoms of heart failure. This is an important reason for the recognition of the earliest toxic effects of the drug, in order that it may be stopped before the onset of vomiting. As Pratt (122) says,

> Vomiting may be preceded by a day or two of complete anorexia, which should be a sign for the immediate discontinuance of the drug, when it seems evident that the anorexia is caused by the digitalis. It is then an indication that the so-called physiologic limit has been reached, and that nausea and vomiting will follow if more digitalis is given. The stoppage of the drug at the first appearance of anorexia does not always prevent vomiting, but it does not, as a rule, last more than a few hours under these conditions. When the drug is administered until vomiting actually occurs, nausea and vomiting may be present for two or three days and occasionally for a week, passing off and recurring several times, even after the drug has been stopped, as Withering observed.

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A difficulty in avoiding nausea and vomiting during digitalis administration is the fact that in some cases, the desired effects of the drug on the heart are obtained with the same dose as that producing the gastric symptoms. Mackenzie (107) noted in his cases that the cardiac effects usually preceded the gastric symptoms, but the two occurred synchronously at times, and Cushny (30) states that minor toxic symptoms, loss of appetite, headache, nausea and vomiting and often diarrhoea usually accompanied the improvement of the circulation produced by the drug. Clinical judgment is the only guide in dealing with individual cases which present this dilemma. Confusion sometimes arises in patients whose stomachs are in a highly irritable state, as is not infrequently seen in heart failure, and who vomit when anything is taken into the stomach. Such patients will often vomit within a few minutes after a dose of digitalis, and then it is safe to say that the drug is not responsible for the vomiting. The reason for this statement will become evident when the mechanism of the emetic action of the digitalis is discussed. Such vomiting should not be taken as a sign for the discontinuance of the drug, as the gastric symptoms may disappear with an improvement of the circulation. A method of administration other than oral may have to be resorted to, however, in such cases.

The relation of the therapeutic use of digitalis to nausea and vomiting has been studied by Eggleston (40) in a series of 15 patients, all of whom were suffering from heart disease. Digitalis was given in the form of the infusion or tincture in the usual or slightly larger doses, as a rule, every four hours. Eleven cases were instances of auricular fibrillation. In this series nausea alone, or nausea and vomiting developed on an average of five days from the beginning of the digitalis administration, when an average of 3.08 grams, corresponding to $7\frac{3}{4}$ drams of the tincture had been taken. In the 4 cases with regular cardiac rhythm, nausea or vomiting occurred in seven days, after the average dose of 2.4 grams of the drug had been given. The average dose in these cases was smaller than that given to the patients with auricular fibrillation. In none of the 15 cases did the onset of nausea or vomiting bear any constant time relation to the administration of the individual doses of the drug. In most cases nausea or vomiting persisted or recurred for some hours after the last dose had been given and the drug withdrawn.

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In estimating the total amount of digitalis which will, on an average, lead to nausea and vomiting, the question of elimination of the drug during the days of its administration must be taken into account, and only rough estimates can be made which have any value when applied generally to patients. Large single doses of digitalis were administered to about 100 patients by Robinson (130), the doses usually ranging from 15 cc. to 25 cc. of a standardized tincture, or 1.5 to 2.5 gram of digitalis. The patients were all adults, and suffered from a variety of cardiac disorders. Only about 10 per cent of these patients showed the toxic gastric symptoms caused by digitalis. Nausea and vomiting came on in these cases in from one-half to one hour after the large doses had been given. Eggleston (40) has collected and tabulated 95 cases from the literature to which digitalis bodies were given in the usual doses until nausea or vomiting appeared. The cases of this series were divided into three groups. The first consisted of cases of auricular fibrillation, the second group of non-fibrillating cases and the third group receiving digitalis bodies other than the leaf. In reviewing the first two groups, it is seen that the dose of digitalis producing nausea or vomiting varies from 1.25 grams to 8.50 grams and the figures are not sufficiently constant to warrant an average of significance to be obtained from them. The dosage falls, however, most often between 2.5 grams and 3.5 grams. A comparison of these two groups of cases leads to the conclusion that the type of heart disease has no direct influence on the amount of digitalis required to produce gastric symptoms, which occur also with approximately the same doses in individuals with normal hearts. The analysis of cases of the third group shows that crystalline digitoxin (Nativelle's digitalin granules), tincture of strophanthus and of squills, and the extract of apocynum also cause nausea and vomiting, when given in sufficient doses. Cushny (30) concluded from clinical observations that digitalis had perhaps less effect on the gastrointestinal tract than strophanthus and squills.

The mechanism by which the digitalis bodies produce their emetic action has been only recently clearly demonstrated, although much speculation and some experimentation had been carried on regarding it. In 1912, Hatcher and Eggleston (75) pointed out that the emetic action of the drug had been generally attributed to its irritant action

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on the gastric mucosa, but that there were several discrepancies between the deductions which had been drawn from animal experiments and the occurrence of nausea and vomiting in patients receiving therapeutic doses of the drug. They observed that the digitalis bodies, as a rule, produced emesis more rapidly and with smaller doses when given intravenously than when introduced into the stomach. In order to eliminate the possibility of action of the drugs during excretion from the blood stream into the stomach, digitalis and several of its allies were injected intravenously into dogs from which the gastro-intestinal tract had been removed. Sixteen of the 21 eviscerated animals went through the motions of vomiting, after the injection of these drugs, and three others showed signs of severe nausea. They injected digitalis, digitoxin, true digitalin, ouabain, strophanthus, amorphous strophanthin and adonis. Hatcher and Eggleston conclude from their experiments that the emetic action of these drugs is exerted upon the vomiting centre in the medulla and is not caused by the local irritation of the gastric mucosa. They consider the purgative action also as obviously of central origin.

Just as this review is going to press, the report of Hatcher and Weiss (78 a) on the emetic action of the digitalis bodies has appeared in a preliminary form. They state that Thumas has shown that the direct application of the digitalis bodies to the vomiting centre in the medulla does not cause emesis. By means of a series of experiments on cats in which various nervous structures were cut, Hatcher and Weiss have shown that digitalis causes emesis only when the nerve supply to the heart is intact. The vomiting centre is not stimulated directly, but by impulses reaching it from the heart, passing up by way of the sympathetic, and to a less, though probably variable extent, by way of the vagus. Ouabain usually failed to produce vomiting after the sympathetic only was cut.

These investigators consider their experiments as evidence that the digitalis bodies induce emesis by reflex action due to irritation of the heart or its appendages. The effect they consider as almost certainly a protective mechanism for the heart such as is recognized in the case of other organs. With the establishment of the fact that emesis is not an effect produced by the direct action of digitalis on certain structures of the medulla, but is secondary to the direct

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action of the drug on the heart, a new attitude must be taken regarding its relation to the cardiac effect of the drug. The effect of the drug on the heart and its effect in producing nausea and vomiting cannot be dissociated and the latter would seem to have a more significant place than has been given to it in evaluating the cardiac action of digitalis.

In a second paper Eggleston and Hatcher (48) investigated the relative emetic activity of a number of more commonly used digitalis bodies and also of several proprietary preparations for which diminished emetic action was claimed. They determined the percentage of the fatal dose required to produce emesis in cats when injected intravenously. The minimal dose and the average of the emetic doses of various digitalis bodies and specialties in percentage of the minimal lethal dose of each drug are given in their paper as follows:

DRUG OR SPECIALTY	EMETIC DOSE IN PERCENTAGE OF FATAL DOSE	
	Minimal	Average
True digitalin	18	22
Strophanthus	27	47
Ouabain	30	49
Digitalis	31	46
Crystalline digitoxin	40	58
Amorphous strophanthin	61	65
Digipuratum	25	42
Fat-free tincture of digitalis	28	34
Digitalysatum	29	36.5
Digalen tablets	29	40
Digalen, liquid	30	38

Eggleston and Hatcher have shown therefore that all these digitalis bodies and preparations have an emetic action which do not differ quantitatively very markedly. True digitalin is the most active emetic, while amorphus strophanthin and digitoxin are the least active in percentage of their fatal doses. There is very little difference between digitalis and various specialties, and these experiments furnish no evidence that digalen, digipuratum, digitalysatum and the fat free tinctures have any advantage over the less expensive galenical preparations of digitalis from the point of view of being

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less disturbing to the stomach when used therapeutically. These authors conclude that there is at present no means of securing the cardiac action of the digitalis bodies without subjecting the vomiting centre to the influence of these agents at the same time, and there is no advantage in substituting one mode of administration, or one member of a group for another, in an attempt to prevent or lessen the gastric symptoms which these drugs cause. They also express their disapproval of the employment of opium as has been advocated to prevent the gastric symptoms, as it may serve to mask the toxic symptoms which should serve as a signal for the discontinuance of the drug or the reduction of the dose.

These experimental studies were followed by the clinical study of Eggleston (40) to which reference has already been made, and in which he correlated clinical experience with the facts of the experiments. He showed in his own series of 15 cases and in 95 cases from the literature, nausea and vomiting almost never occur as a result of digitalis until it had been absorbed sufficiently to produce its characteristic effect on the heart. His study shows that there is no valid evidence that therapeutic doses of the digitalis bodies cause nausea or vomiting through local irritation on the alimentary tract, but that there is strong evidence to the contrary. He concludes, therefore, that the nausea and vomiting resulting from the therapeutic use of digitalis and its allies in man are due to their direct action on the vomiting center in the medulla. Eggleston draws the deduction from his conclusions that preparations which fail to produce nausea and vomiting when administered in large doses are either weaker than those that do produce these effects or are less well absorbed.

Vomiting may be considered as a desirable effect from one point of view, as it may prevent further toxic symptoms from following an overdose of the drug when taken by mouth, as part of the drug may be eliminated when the stomach is emptied by the vomiting which it produces.

The purgative action of digitalis has not been prominently described in recent clinical studies, and its absence was noted in the 42 patients carefully studied by Mackenzie (107) to whom sufficient digitalis was given so that gastric symptoms usually occurred. He found,

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however, that diarrhoea was produced by strophanthus and squills. Bastedo (5) also noted that diarrhea is much less frequent than anorexia, nausea and vomiting as a sign of overdose in digitalis administration. The writer's experience confirms these statements.

2. Toxic effects on the heart

Although the gastric disturbances are the most obvious unfavorable effects of digitalis, the cardiac disturbances must be regarded as the most serious in the clinical use of the drug. It is the direct effect of digitalis on the heart which produces death in animals to which a lethal dose is administered, and certain disturbances of the heart-beat resulting from an overdose of the drug to man must always be considered as the forerunner of effects which profoundly lower the efficiency of the circulation and which render the heart eventually incapable of maintaining the circulation. For this reason, the early recognition of the unfavorable effects of the drug on the heart is a matter of paramount importance.

When Cushny (28) first studied the effect of digitalis on dogs by a method that allowed the activity of auricles and of ventricles to be distinguished in graphic records, he discovered early effects which he attributed to the stimulating action of the drug on the vagus centre and later effects which he considered as the result of the direct action of the digitalis on the heart muscle. These later effects, constituting the second stage of digitalis action, were attributed mainly to an increase in the irritability of the myocardium.

Robinson and Wilson (134) administered digitalis intravenously to cats and followed the effect of the drug on the heart by electrocardiograms. It was found that when about 75 per cent of the lethal dose was administered, evidence of increased irritability of the ventricles appeared, manifesting itself as premature contractions which were soon followed by idioventricular rhythm, when cardiac impulses were being generated at a more rapid rate in the ventricles than in the auricles. This state of affairs was followed, during further administration of the drug, by ventricular fibrillation and death.

More recently Levine and Cunningham (94) using the same methods have found that when various preparations of digitalis were injected

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into cats, premature ventricular contractions or extrasystoles appeared when an average of 48 per cent of the lethal dose was administered, and they considered the appearance of this phenomenon to mark the onset of increased ventricular irritability. They used the appearance of ventricular extrasystoles therefore as evidence of the first toxic sign of digitalis.

The analysis of unfavorable effects of the drug on the heart when administered to man had its inception with the first of Mackenzie's studies published in 1905, when he described the bigeminal pulse and recognized that its production resulted from frequent ventricular extrasystoles. He also showed that the conduction of the cardiac impulse is disturbed by the drug. In 1911, Mackenzie pointed out that digitalis may cause irregularities of impulse production, extrasystoles, partial heart-block, and pulsus alternans. The cardiac manifestations of overdose in digitalis administration were studied by Bastedo (5) who made polygraphic records of patients receiving the drug, and demonstrated the occurrence of auricular and ventricular extrasystoles, partial heart-block, paroxysmal trachycardia and possibly pulsus alternans. Bastedo recommends that digitalis be discontinued whenever the radial impulse rate goes below 60 per minute, whenever sudden slowing of the heart rate indicates the occurrence of heart block, whenever a regular ventricular rhythm becomes irregular, whenever tachycardia occurs or whenever coupled rhythm or phasic arrythmia appear in hearts showing auricular fibrillation.

a. Premature contractions. The two outstanding disturbances of the cardiac mechanism which digitalis causes in patients are those resulting from increased irritability of the ventricles and from depression of the conduction of the cardiac impulse from auricles to ventricles. The effect of digitalis on the ventricles leads to the occurrence of *premature contractions* of ventricular origin, commonly called extrasystoles. They are, generally speaking, always detrimental to the efficiency of the heart. Premature ventricular contractions tend to occur in diseased hearts and are, in many patients needing digitalis, readily provoked by relatively small doses of the drug. They appear to be provoked especially readily in patients with auricular fibrillation, when coupled rhythm replaces the absolutely

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irregular cardiac action. At times these premature beats occur so frequently after small amounts of digitalis that it is the better part of judgment to discontinue or diminish its use before the optimum therapeutic effects are obtained.

The occurrence of ventricular premature beats may be readily recognized by the stethoscope with the finger on the pulse when they occur in hearts beating otherwise regularly. Except when definite coupled beats occur, it is impossible to recognize premature ventricular contractions however in cases of auricular fibrillation without electrocardiograms, which alone show, by the variations in form of the ventricular complexes, that some of the cardiac contractions are arising from ectopic points in the ventricles. The frequent occurrence of ectopic ventricular contractions during the use of digitalis in auricular fibrillation may be sometimes responsible for the failure to get the ventricular slowing that the drug usually produces in these cases.

There is a great difference in patients as to the amount of the drug which causes the onset of premature ventricular contractions, and no statement as to the average amount required can be made. It is evident, however, that in many patients ventricular contractions occur with an amount of the drug which is a much smaller proportion of the lethal dose than has been observed during the intravenous administration of the drug to cats.

Edens and Huber (38) have discussed the production of premature ventricular contractions by digitalis, and the occurrence of the bigeminal pulse. They consider it probable that the bigeminal pulse follows the administration of digitalis only in hypertrophied hearts with lowered muscular efficiency. They believe that the production of the bigeminal pulse by digitalis is an unfavorable prognostic sign. They also point out the great variability in the size of the dose which brings about the bigeminal pulse. Although their ideas regarding the relation of cardiac hypertrophy and inefficiency to the digitalis bigeminal pulse have not been confirmed, it is a point worthy of close attention.

The frequency of apparently spontaneous premature beats may lead to some difficulty in fixing the responsibility for them during digitalis administration, but it should be emphasized that it is a

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definitely established fact that they may be caused directly by digitalis, and should always be considered as a probable toxic effect whenever they occur during the administration of any member of the digitalis group. The influence of digitalis on apparently spontaneous premature contractions will be discussed later.

The production of the so-called auriculo-ventricular rhythm by digitalis is an effect of the drug closely related to the production of premature ventricular contractions. This type of disturbed cardiac mechanism has been observed by Cohn (20) to follow the administration of digitalis and to disappear when digitalis had been completely eliminated. In auriculo-ventricular rhythm, the auricles and ventricles beat independently but each at nearly equal rates. Electrocardiograms indicate that the auricular stimulation is not usually disturbed, while the auriculo-ventricular node (of Tawara) assumes the rôle of ventricular pace-maker, by generating stimuli at a slightly faster rate than the sino-auricular node. Auriculo-ventricular rhythm is associated only with various forms of cardiac intoxicants, notably digitalis.

b. Depression of conduction of the cardiac impulse from auricles to ventricles is one of the most striking effects of digitalis, which may lead to partial or complete heart-block. This action of the drug is generally considered to result, for the most part, from its stimulating effect on the cardio-inhibitory mechanism, although there is not entire agreement as to the relation of this effect to the direct action of the drug on the cardiac tissues.

The great value of digitalis in certain forms of heart disease depends largely upon its ability to block impulses in their passage from auricles to ventricles, and for this reason the action of digitalis on conduction will be discussed when the therapeutic effects of the drug are considered. On the other hand, heart-block produced by the administration of digitalis may definitely lower the efficiency of the circulation, and it must be considered therefore as a toxic manifestation of the drug. Its recognition and the means of avoiding its production will be briefly discussed at this time.

Mackenzie (106) first demonstrated heart-block as an effect of digitalis in man in 1905. Since that time, the influence of digitalis on conduction has been extensively studied by graphic methods.

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As Bastedo (5) has pointed out, when a rapidly beating heart becomes suddenly slowed during the administration of the drug or if an intermittent cardiac rhythm unassociated with premature beats develops, it is safe to infer that heart-block exists. These events should be taken as indications for discontinuing the administration of digitalis.

Uncertainty of the diagnosis of heart-block will always exist, however, without the employment of the polygraph or the electrocardiograph. It is only by these methods that the earlier effects of digitalis on conduction, when the cardiac impulses are merely delayed in their passage from auricles to ventricles, can be detected. It is distinctly advantageous, therefore, to employ these methods during the administration of digitalis in order to detect its effect on conduction before a stage is reached which may lower the efficiency of the heart.

A number of students of digitalis, among whom are Edens (37) and Cushny (29) have expressed the opinion that digitalis affects especially the conducting system of heart in which auriculo-ventricular conduction has been previously damaged by disease. Although Cohn and Fraser (22) have shown that this is by no means a necessary condition for the production of digitalis heart-block, it must be a predisposing factor in some instances. It is very desirable to know the functional state of the conducting system before the administration of the drug to patients with heart disease, and this information is furnished by measuring the time between the onset of auricular activity and ventricular activity. When this time is found delayed beyond the normal limits, it should be taken as a contraindication for the use of digitalis or it should call for caution, careful observation, and alteration of dosage.

R. H. Halsey (64) has reported a case showing profound effects brought on apparently by excessive vagus stimulation producing severe subjective symptoms. Following the administration of digitalis to a patient with auricular fibrillation, severe cardiac failure and Cheyne-Stokes breathing, marked variation in the ventricular rate from 100 to 50 beats per minute were observed, the rapid rate occurring during the periods of apnea. This phenomenon apparently interfered with the interchange of O_2 and CO_2, and was relieved by atropin when the ventricular rate became 150 per minute.

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Windle (161) studied the comparative effects of digitalis, strophanthus, squill and apocynum on the conduction of cardiac impulses in a case of mitral stenosis which required treatment on four occasions. He used a different drug each time, the tincture of each being employed. Apocynum had no effect on conduction, while the other three drugs caused partial heart-block with approximately equal amounts.

630 minims of the tincture of digitalis were given in 14 days
540 minims of the tincture of strophanthus were given in 19 days
480 minims of the tincture of squill were given in 4 days.

When heart-block was observed in each instance it is evident that these three members of the digitalis group required total amounts which are comparable to produce partial heart-block in this case, although the rate of administration was different.

c. Other disturbances of the heart beat have been observed occasionally following large doses of digitalis. The auricles are affected, although less frequently, in the same manner as the ventricles, and premature auricular beats sometimes occur during the digitalis administration, presumably as a result of the action of the drug. Bastedo (5) has reported a case of paroxysmal tachycardia which he considered as produced by digitalis, but the relation of the inception of this disturbed cardiac mechanism and the action of the drug seems uncertain.

Special interest is attached to the influence digitalis may have in causing auricular fibrillation. Cushny (30) has stated that digitalis may cause the onset of auricular fibrillation and Danielopolu (33) has reported three cases in which auricular fibrillation followed the administration of the drug, in each instance the onset of fibrillation occurring coincidently with the maximum digitalis action. Danielopolu considered that in his cases the auricles were predisposed to fibrillation which was provoked by the stimulating effect of the drug on the vagus. Mackenzie (107) has reported a case in which auricular fibrillation set in at the time when an amount of digitalis sufficient to cause maximal effects had been given, and disappeared four days after the discontinuance of the drug. Robinson (126) studied a case of paroxysmal auricular fibrillation to whom digitalis was administered, but was unable to draw any definite conclusion

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as to the influence of the drug on the persistence of the fibrillation. Agassiz (2) administered strophanthin intravenously to such a case, with the result of apparently prolonging the paroxysm of auricular fibrillation, although the ventricular rate was slowed by the drug. It is these cases of transient auricular fibrillation in which the question of the relation of the drug to the production of this cardiac disturbance is especially important. The evidence seems sufficient, as Fulton (56) points out, to warrant the conclusion that digitalis does predispose the auricles to fibrillation, and its use may therefore be disadvantageous in cases where it is desirable to prevent recurrent attacks of fibrillation, or where a cessation of fibrillation may be expected, although the drug may be very useful when fibrillation is present. Clinical judgment can be the only guide under such conditions.

Auricular standstill has been observed by White (157) as an effect of digitalis in cases of heart disease. In these cases, both electrocardiograms and graphic records from the jugular vein failed to show any evidence of auricular activity during the height of digitalis action. In all three cases, the auricular activity returned when the effects of the drug passed off. White considers this phenomenon as a rare result of digitalis administration, and no other similar cases are to be found in the literature. Atropin was administered in one case, but had no effect upon the cardiac mechanism except for a slight increase of rate.

White and Sattler (160) have also described a curious arrhythmia consisting of blocked auricular premature beats occurring in a healthy subject after 3 grams of digitalis had been taken. *Sinus arrhythmia* in which the rhythm of impulse formation is disturbed, is commonly observed with large doses of digitalis, as first pointed out by Wenckebach (155). A number of cases of *sino-auricular block* produced by digitalis have also been observed by the electrocardiographic method, as a result of digitalis action.

Pulsus alternans, a condition in which the regularly beating ventricles contract with alternating force, is generally considered a sign of disturbed contractility of the heart muscle, and of serious prognostic significance. Mackenzie (107) and Windle (162) each state that they have observed this phenomenon as a sequel of digitalis administration in two cases. Bastedo (5) reports one case

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which he considered as possibly pulsus alternans produced by digitalis, but his records do not allow him to make a definite diagnosis, and his published curves are not characteristic of this condition. These cases are important as an indication that digitalis may affect the heart muscle, presumably directly, in such a way as to lower its efficiency. Bastedo believes that pulsus alternans results from a constriction of the coronary arteries produced by digitalis, but this idea must be considered purely hypothetical, as there are no definite facts to support it.

Weil (154) has brought forward a criterion for the early recognition of digitalis intoxication which is somewhat different from those that have already been mentioned. He has shown that, under the influence of the drug, the heart becomes more responsive to pressure over the vagus nerves in the neck, and he believes that a well marked vagus response during digitalis administration in a heart which was previously less responsive may be used as indicating the onset of toxic digitalis effects.

3. Fatalities resulting from digitalis bodies.

It is not within the scope of this review to discuss fatalities resulting from amounts of digitalis far in excess of those used for therapeutic purposes. According to Sollmann (143) 2.5 grams of digitalis have proved fatal when taken at one dose, while 4 grams have been followed by recovery. Sollmann states that the symptoms of a fatal dose are those of "cumulation"—gastro-intestinal disturbances, slow and arrhythmic pulse, etc., lassitude, muscular weakness and sensory derangement. Death generally occurs suddenly, with dyspneic convulsions. Consciousness persists late.

Sudden death has been seen occasionally following the administration of the drug in the treatment of heart disease, and fatalities occurring under these conditions must be considered as possibly caused by the drug. During the administration of digitalis by mouth in the usual doses, it is difficult to say what rôle the drug might play as a cause of sudden death. Since the introduction of the intravenous method of administration, however, fatalities have apparently resulted from the injection of the digitalis bodies into a vein. These have most often followed the use of strophanthin, and according to inquiries made by

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the writer, have been seen more often than the literature would make one believe. Bastedo (5) remarks that he has heard of one death following the intravenous injection of digitalis in a man and of several such fatalities occurring in from three minutes to an hour after the injection of strophanthin. The writer has observed 1 case in which death occurred suddenly about five minutes after 1 mgm. of strophanthin was given intravenously, and at least 3 other such cases have been related to him by others. Recently Rahn (123a) has reported 2 fatalities following intravenous injections of strophanthin and has reviewed 16 other cases collected from the literature in which death occurred in such close connection with the intravenous injection of the drug as to make a relation of cause and effect seem very likely. In 11 of the cases the causal relation seems certain. Rahn discusses the clinical significance of these deaths and is of the opinion that some of these could have been avoided by smaller doses, longer intervals between doses and a better knowledge of previous administration of digitalis. He believes that the drug should be given by this method only after careful study of the patient. The sudden fatal termination and the relatively short interval between the injection and death seen in a number of these cases leads to the conclusion that strophanthin caused the ventricles to fibrillate, a cardiac state incompatible with life. Ventricular fibrillation is the final stage of cardiac intoxication in most cases when the digitalis bodies are injected intravenously into cats, as shown by Robinson and Wilson (134) and by Levine (92). It is likely that the fatal cases under discussion occurred in patients in whom cardiac damage had already rendered the ventricles prone to fibrillation.

Garrey (57) has investigated the underlying factors responsible for fibrillation of the cardiac muscle, and has advanced an explanation of this phenomenon on the basis of his experiments. The essential points in Garrey's conception of fibrillation are these. Fibrillary contractions of the heart muscle depend upon the establishment within the musculature of multiple regions of block or impaired conductivity. The impulses thus blocked or delayed take abnormal or circuitous paths, and return to the same portion of the muscle after the refractory state has passed off, but while other portions are still refractory. The latter portions are subsequently involved in a

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similar manner, and the whole tissue mass is then thrown into a continuous incoördinated contraction, which is not initiated or sustained by new impulses arising from any definite location.

With these points in mind it seems reasonable to consider evidence of impaired conduction within the ventricles as a contraindication to the intravenous use of full doses of strophanthin or other digitalis bodies. Such evidence is sometimes obtained by the study of electrocardiograms, as certain abnormalities in the form of the ventricular complexes indicate delay or abnormal conduction routes in the ventricles. The bearing of these abnormal complexes to the administration of strophanthin has been discussed by Robinson and Bredeck (131), who express the opinion that such electrocardiographic findings should be taken as a contraindication to the intravenous use of strophanthin, and they show the relation these abnormal electrocardiograms may have to ventricular fibrillation.

Although the danger entailed in the intravenous administration of strophanthin has been generally recognized, other digitalis bodies have not received as much consideration from this point of view. Levine and Cunningham (94) however have studied the so-called margin of safety of intravenous digitalis administration in cats, and draw certain conclusions from their experiments bearing on the intravenous use of the drug. They determined the percentage of the lethal dose which produced the earliest demonstrable toxic signs. The minimal toxic dose was calculated in their experiments as the smallest dose that is required to produce ventricular extrasystoles, demonstrable by electrocardiograms. The margin of safety was taken as the difference between the minimal lethal dose and the minimal toxic dose. They have introduced

> the concept of the margin of safety of digitalis preparations because, in the practical use of the drug, the therapeutic dose is very close to the toxic dose. Therefore, it is of great importance to know how far removed the lethal dose is from the toxic dose, and whether the margin is greater in some preparations than in others.

They used aqueous extracts of several different samples of leaves, several different tinctures, and ampoules of Digifoline, Digalen and Digipuratum. They found considerable variations in different

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animals both in susceptibility to the drug and in the margin of safety which varied from 27 to 64 per cent. The average margin of safety, however (the difference between the percentage causing death and that causing earliest evidence of toxicity), was 48 per cent of the lethal dose. This difference is identical with the results which Levine (92) obtained in previous work with crystalline strophanthin or ouabain. Levine and Cunningham (94) state on the basis of their findings that

> the practical consideration that follows from these experiments is that although the various digitalis bodies, when given by mouth, are generally regarded as much safer than intravenous administration of strophanthin, when the entire digitalis glucosides (either the aqueous or the alcoholic extracts) are given intravenously, the same risk is encountered as in using strophantin.

They found also but little difference in the rapidity with which the various digitalis bodies and crystalline strophanthin act on the heart when introduced directly into the circulation.

If these experiments can be applied to man, and it seems only safe to assume that they can, it must be borne in mind that the risk of introducing digitalis directly into a vein appears to be as great as when strophanthin is used.

The question of the percentage of the lethal dose which is employed in the treatment of heart disease has been discussed by Robinson and Wilson (134) in the light of their experiments in which the tincture of digitalis was administered intravenously to cats. They consider the inversion of the T wave of the electrocardiogram the digitalis effect offering the most useful comparison of the effects of the drug on the cat's heart and the effects obtained in man. The T wave became inverted in their experiments when from 20 to 30 per cent of the lethal dose had been injected. The maximum therapeutic effects of digitalis usually occur with a dose not much in excess of the amount sufficient to cause inversion of the T wave. Robinson and Wilson, taking these facts into consideration, have expressed as their opinion that the maximum therapeutic effects are probably produced in man by the administration of from 30 to 40 per cent at most of the lethal dose of the drug.

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VIII. THE THERAPEUTIC EFFECTS

The beneficial effects exerted by the digitalis bodies upon patients suffering from heart disease are dependent, not upon a single mode of action of the drug on a single organ, but upon a combination of effects. The relative importance of the various activities of digitalis in its therapeutic use has been the subject of much controversy for many years, and although much of this controversy has been cleared up, several points remain about which there is no unanimity of opinion. As has been stated, animal experimentation has added confusion, in some respects, to the problem of determining how digitalis benefits patients with heart disease, and the question can receive its final answer only by the study of patients.

The various effects which may enter into the therapeutic action of digitalis will be discussed separately and their relative importance will be considered in connection with the use of the drug in various forms of heart disease.

1. The effect on the heart muscle.

a. The effect on ventricular contraction. The relation of the effect of digitalis on ventricular contractions to its beneficial influence in heart disease has been much discussed, but this problem has not yet been definitely solved. Its solution is difficult, partly because there has been no certain means of measuring the direct influence of the drug on the efficiency of the heart muscle, and partly because the various factors entering into the therapeutic action of the drug cannot be sharply differentiated from one another. In spite of the uncertainty which actually exists, digitalis has been generally considered for many years as a so-called "heart tonic," and its beneficial effect has been considered as mainly due to an increased output of the heart by its action on the muscle itself.

The older conception is well illustrated by a statement made by Balfour in his clinical lectures on Disease of the Heart, quoted by Schmoll (141).

> All the benefits we obtain from digitalis are inseparably connected with its tonic action; they flow from the power that digitalis has of increasing muscular activity, and the improved metabolism of all the tissues, but especially of the myocardium.

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Schmoll expresses his belief that the drug acts as a specific by its effect on the tonicity of the heart muscle.

Schmiedeberg (140) basing his opinion apparently on the results of animal experiments states in the seventh edition of his text book, that the therapeutic action of digitalis is due almost exclusively to its effect on the heart muscle. He considers an increase in the elasticity of the heart muscle the most important effect of the drug and that the change in elasticity is also responsible for the systolic standstill of the heart produced by the drug. Schmiedeberg believes that all other effects of digitalis are mainly secondary to the increased force of the cardiac contractions which the drug calls forth.

Other students of the effects of digitalis on animals, notably Cushny, have found that the drug causes an increase in the output of the mammalian heart under experimental conditions, which occurs in excess of that which results from the slowing of the heart rate alone.

Another experimental pharmacologist Gottlieb (59) states that the work of a single contraction of the isolated mammalian heart may increase under the influence of digitalis two and a half to three times, and Gottlieb summarizes his conception of the therapeutic action of digitalis as due principally to more complete contraction of the ventricles and re-distribution of the blood in the vessels. He believes the drug may strengthen the contractions of the "weakened heart."

It does not seem profitable to enter into a discussion of the experimental studies of this subject, as the conditions under which facts have been adduced are not applicable to a consideration of the therapeutic action of digitalis. In this connection, Cohn (20) has said

> Those effects reported earlier, of changes in the magnitude of ventricular contractions gained in experiments, are more recently admitted (Joseph) to have been obtained by doses far too great. The much smaller doses now used are still much larger than are permitted in therapeutics, but even these fail to show marked changes in the extent of the excursion of the ventricular wall which was formerly held to indicate the nature of effective digitalization. The methods employed in pharmacology are not superior to those now available in clinical medicine. Both are on a par in respect to obtaining objective records of this phase of digitalis action.

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In the absence of accurate means of measuring the therapeutic action on the heart muscle, the opinion of various clinical investigators must be considered more as impressions than as well founded convictions. In Mackenzie's (106) first studies on digitalis, he says that the good effect on the cardiac contractions may be due to the slowing of the cardiac rate, but under certain circumstances, the fact that digitalis may effect the function of contractability directly can be demonstrated in a most striking and convincing manner. In his later clinical studies, however, when he was in possession of a more extensive knowledge of the cardiac mechanism and its derangements, he stated that he was unable to determine that the drug affected the heart muscle, but admits that changes may take place in the heart which we cannot detect.

Wenckebach (155) believes that digitalis increases the strength of the human heart by its direct action on the heart muscle, but that there is no evidence that the drug acts on the obscure property, tone of the muscle. Edens (37) has advanced the hypothesis that the poor nutritional condition of the myocardium which is presumably present in heart disease tends to prevent digitalis from exerting its effort on the cardiac contractions, and offers this explanation for his inability to observe any direct action on the heart muscle. Cohn (20) in speaking of the effects of the drug when administered to patients in doses calculated to produce the optimum effects in heart disease stated in 1915, "that if digitalis increases the ability of the ventricles to pump blood, it does so by means of a change which is more subtle than can be distinguished by our methods."

With this limitation of the knowledge regarding this important factor in explaining the action of digitalis in mind, Cohn and Levy (26) have undertaken an investigation of the effect of therapeutic doses of digitalis on the contraction of heart muscle by means of animal experiments. They have been careful to use doses of the drug which were comparable in percentage of the lethal dose to those administered to patients. The tincture of digitalis and g-strophanthin were injected intravenously into dogs and cats, and alterations in volume output were studied in curves obtained by the use of the Roy and Adami myocardiograph.

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The curves represent longitudinal linear alterations in the form of ventricles, and may, under the condition of cardiac contraction, represent changes in volume of the cavities and consequently of volume output. The results are reported as changes in the degree of contraction.

In 30 dogs, they obtained increased contractions 24 times; while other phenomena of digitalization revealed by electrocardiograms were less constantly observed. In 14 cats the degree of contraction increased 4 times, decreased 6 times and was unchanged 4 times, with even more frequent effects on electrocardiograms than in dogs. The effect on contraction differed, therefore, in cats and dogs. Blood pressure readings were also made in some of the experiments in which ether was administered and the chest opened. In order to rule out the effect of these procedures, several experiments were performed on unetherized dogs without operative procedures; the blood pressure being obtained from the carotid artery which had been previously freed from the tissues of the neck (van Leersum's method). In these experiments the electrocardiographic and blood pressure changes were similar to those of the dogs on which operations were performed. From these experiments, the conclusions are drawn that digitalis and strophanthin with doses of therapeutic range increase the contractile power of the cardiac muscle, and by so doing, increase the volume output. This result supplies a firm basis for the statement that these drugs may exercise a beneficial action on the normally beating heart by their action directly on the cardiac muscle. Their results regarding blood pressure and electrocardiography will be mentioned when these phases of the digitalis problem are considered.

b. The effect on the electrocardiogram. The effect of digitalis on the T wave of the human electrocardiogram has furnished evidence of a different kind from that which has been discussed, and it has served as apparently clear proof that the drug acts directly on the heart muscle when administered in therapeutic doses. Although no direct relation has been established between the change in the T wave and the efficiency of the cardiac action, the discovery of this effect has been very useful in studying digitalis and has marked a definite advance in our knowledge.

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Cohn and Fraser (22) first reported briefly in 1913 that they had "found that as the result of digitalis intoxication, the T wave in the electrocardiogram often becomes negative or diphasic, but returns to normal after the effect of the drug has passed off. It is an interesting fact that, although atropin may cause rate and conduction to return to normal, this change in the electrocardiogram persists."

The influence of digitalis on the T wave of the electrocardiogram was studied in a series of patients by Cohn, Fraser and Jamieson (23) who made the first comprehensive report on this subject, although a number of scattered observations on animals and man had been previously reported by others. Cohn and his coworkers found that an alteration of the T wave occurred in 30 of 34 patients to whom full doses of digitalis were given, and that this alteration was generally observed before alterations in rhythm or conduction time had occurred or before gastro-intestinal symptoms disturbed the patients. For the most part, the changes in the T wave consisted, first, in a diminution in the height of the wave, and finally in an inversion. In cases yielding downwardly directed T waves before treatment, digitalis produced eventually upwardly directed waves and other variations in the T waves occurred. This portion of the electrocardiogram was affected in patients with auricular fibrillation and flutter, and in one patient with complete auriculo-ventricular dissociation, as well as in those with normally beating hearts. It is pointed out that the sign attains greater importance on account of its appearance early after the beginning of the administration of the drug. Changes in the T wave were detected after an equivalent of 1.2 grams or even less of the dried leaves of digitalis had been given.

The influence of atropin on the altered T wave was repeatedly tested, and full doses of the drug intensified the changes in the T wave during its transient action. Atropin alone, however, produced no changes in the T wave. The altered T wave persisted for some days after digitalis was discontinued, resembling, in this respect, other effects of the drug.

In discussing their results, Cohn, Fraser and Jamieson bring forward convincing arguments to prove that the alteration of the T wave is caused by the action of digitalis on the heart muscle. The effect that atropin has on the phenomenon indicate, however, that

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the cardiac inhibitors, the vagus nerves, are capable of exerting an influence upon it. The effect of full doses of digitalis on the T wave of the electrocardiogram of healthy children was studied by McCulloch and Rupe (112). They found that the drug did not produce the same effects as readily or as frequently as in adults as shown by the observations of Cohn, Fraser and Jamieson, although larger amounts of the drug per unit of body weight were given to the children, and other evidence of digitalis action was abundant.

Since the appearance of the paper by Cohn and his coworkers, their results have been abundantly confirmed, both for man and animals. Robinson and Wilson (134) found the inversion of the T wave was the first constant sign of digitalis action to be detected by electrocardiograms when the drug was injected intravenously into cats. It occurred in their series when approximately 25 per cent of the minimum lethal dose had been injected, and the dosage necessary for its production was not altered when the vagi were cut.

Cohn and Levy (25) have recently compared the effects on patients of g-strophanthin given intravenously with the effects of comparable doses of digitalis (digipuratum) given by mouth. Only a preliminary report has been published. They studied the relative effect of the two drugs on the T wave of the electrocardiogram and found that strophanthin had little or no influence on the form of the T wave, which at most underwent only transient changes, while the usual effects were produced by digitalis.

c. The effect on the size of the ventricles. Several attempts have been made to determine whether the administration of digitalis leads to the development of *hypertrophy of the ventricles.* Cloetta (18) found that the continuous subcutaneous administration of digitalis to young rabbits had absolutely no effect upon the size of their hearts, as compared with a series of controls. Of a series of animals in which aortic insufficiency was artificially produced, those treated with digitalis showed less cardiac enlargement than those that were not treated.

Caro (12), on the other hand, noted cardiac hypertrophy in animals to which digitalis had been given over a long period of time as did Reinike (125) who compared the cardiac muscle with the skeletal muscles. The latter muscles did not participate in the hypertrophy

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observed in the heart. This work is based on a very small number of animals (four rabbits and two dogs) and so the conclusions drawn can hardly be considered as justified. Gelbart (58) repeated Cloetta's experiments with rabbits in which aortic insufficiency was artificially produced, and found that four weeks after the valve damage, cardiac hypertrophy had developed which was, in no way, influenced by digitalis. In view of the conflicting evidence, the relation of digitalis to cardiac hypertrophy must be considered as an open question.

The influence of digitalis on *cardiac dilatation* presents an important question. Although ventricular dilatation may be favorably effected by the administration of the drug it is impossible to say whether this result is brought about by direct action on the heart muscle or whether it is secondary to other beneficial effects.

d. Chemical aspects of digitalis action. The action of digitalis on the cardiac muscle has been studied from *the chemical view-point* by Burridge (8), who made some pioneer contributions which may bring results of fundamental importance to the therapeutic use of digitalis in the future. He has concerned himself especially with the interaction of digitalis and calcium on the perfused heart. He studied changes in the degree of cardiac contractions resulting from changes in the calcium content of the perfusion fluid. During some observations on the cardiac reserve, he found that calcium determines the amplitude or the percentage of the contractile material possessed by the heart which is used up with each spontaneous beat. And further that, under certain conditions, digitalis is a drug which enables a given tension of calcium in the perfusion fluid to evoke the activity of a greater proportion of the whole contractile material than is the case in its absence.

Burridge (9), in a second paper, discusses some factors of the cardiac mechanism illustrated by reference to certain actions of barium and digitalis. He interprets his experiments to mean that digitalis renders the heart more susceptible to calcium, as a given amount of calcium had more effect on the heart after treatment with digitalis than before. Crystalline digitoxin was used. He studied (*a*) the effect of digitalis on changes in the amplitude of contractions with fixed amounts of calcium, and with amounts of calcium necessary to evoke a fixed proportion of the whole contractile material;

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(*b*) on the amount of tonus produced by a given amount of calcium and vice versa; and (*c*) on the amount of shortening of the refractory period produced by a given amount of calcium. Not only was calcium more effective but less calcium was required to produce constant effects after the heart had been exposed to digitalis. The response of the heart to calcium could be increased five to tenfold by treating it with digitalis, the effects of which persisted after the drug was withdrawn. The amount of calcium necessary to allow normal contractions may produce systolic standstill of a digitalized heart. A difference was noted in this respect, however, in hearts that had been long perfused and in fresh hearts, digitalis causing more marked effects in the latter.

Burridge believes that digitalis may be considered as a cardiac "lubricant," and should be classed with the secretions of the adrenals and pituitary gland in this regard.

Loewi (104) has also studied the relation of the effects of calcium and digitalis. He is of the opinion that in cases of heart disease the capacity of the heart for stimulation by the physiological calcium content of the blood is depressed. Strophanthin, Loewi believes, brings the sensitiveness of the heart to calcium back to normal.

These studies on the perfused heart represent conditions so far removed from those obtained in the treatment of heart disease that direct application is unwarranted. On the other hand, the work of Burridge and Loewi is very interesting and should not be lost sight of in attempts to find the fundamental principles underlying the action of digitalis on the human heart.

Levine (92) has discussed the question of whether the action of the digitalis bodies on the heart is a physical or a chemical process. His review of the work bearing on this question shows how difficult it is to find its answer. Certain facts indicate that probably chemical changes and physical action each play a part. The general condition of the heart, the temperature, rate and pressure of the perfusion system, and its organic and inorganic constituents are all factors difficult to resolve. Levine's perfusion experiments with strophanthin-g have led him to believe that the heart utilizes only a small portion (in the neighborhood of 10 per cent) of the drug to which it is exposed, regardless of the concentration at which it reaches the heart.

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A toxic effect results when the heart has taken up a certain total of the drug, which is a definite small fraction of its own weight. If this theory be correct, it explains why, in concentrated solutions, the total amount is not important, for the small part that is taken out by the heart does not appreciably alter the concentration, while when very dilute solutions or small quantities are used, the amount taken up by the heart diminishes the remaining concentration appreciably; that is, the "digitalis pressure" becomes lessened. In these experiments, the rapid injections forced an adequate amount of strophanthin into the heart rapidly, and produced the toxic effect; in the slow injections, the same total amount of the drug was taken up by the heart, only more slowly.

2. The effect on the cardio-inhibitory mechanism.

Since the demonstration by the Weber brothers of the cardio-inhibitory mechanism, much interest has been shown in its relation to the action of drugs affecting the heart, and pharmacologists have had to take into account the possibility of indirect action of drugs on the heart through its nervous mechanism. The illuminating analysis of the cardiac action of the vagi by Engelmann has been of much value in attempts to understand the action of drugs affecting the heart. He showed that the heart possessed the properties of contractility, conductivity, rhythmicity and irritability, and that all these properties were depressed when the vagus nerves were stimulated. This conception has not only done much to form a basis for the explanation of abnormalities of the heart beat, but it has also been useful in understanding the effects that digitalis exerts on the heart.

a. Vagus stimulation. Traube was the first experimenter to find that cutting the vagus nerves altered the effect of digitalis on the heart. His later studies led him to conclude that digitalis stimulated the cardio-inhibitory centre in the medulla, and affected the heart through the vagi. Ackermann, according to Boehm (6) demonstrated in 1871 that digitalis failed to slow the heart of animals after atropin had been injected. Boehm, who was also one of the earliest experimenters with digitalis, concluded from his work with frogs, that the drug heightened the irritability of an inhibitory centre in the heart, and thus increased the susceptibility of the heart to vagus action.

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Cushny (29) made an important contribution to the action of digitalis by his studies on the mammalian heart. He showed that the drug acted both by direct action on the muscle and by stimulation of the cardio-inhibitory centre. He divided its action into the inhibitory and the muscular stages, and concluded that the beneficial stage of its effect in heart disease resulted from its action on the heart muscle, while its inhibitory action was undesirable from the therapeutic standpoint. The fact that digitalis has two modes of action on the heart has made it difficult to reach definite conclusions as to their relative importance, and to give a clear conception of its effects.

Although the vagus effects of digitalis have been considered by most students of the subject to result entirely from the direct stimulation the cardio-inhibitory centre, other opinions have been held. Schmiedeberg (140) considers that vagus stimulation is secondary to the increased blood flow produced by the action of digitalis on the heart muscle. Kockmann (89) concluded from his experiments on dogs that digitalis causes slowing of the heart at least in part by stimulation of the peripheral end of the vagi. He obtained cardiac slowing in dogs by intravenous injections of various digitalis bodies after the vagi had been cut and found that this slowing was replaced by acceleration when atropin was given. Etienne (50) repeated these experiments and was unable to confirm Kockmann's observations.

Green and Peeler (60) studied the action of digitalis on the cardio-inhibitory centre when perfused through the isolated head and brain of the turtle. In their experiments, the head was completely isolated from the general circulation, and all tissues in the neck region except the vagus nerves were severed; the connection through the nerves being the only one maintained between the head and the body. The cardiac movements were recorded by a direct attachment of the ventricular apex to the recording lever. They found that when digitalis was perfused through the turtle's brain, the cardio-inhibitory centre was strongly stimulated and that not only was the rhythm of the heart inhibited, but the conduction of the cardiac impulses was also depressed. The weight of evidence is strongly in favor, therefore, of the conception that the vagus effects of digitalis on the heart are mainly or entirely the result of the direct stimulation of the cardio-inhibitory centre, although other factors may take some minor part in their production.

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b. The effect on cardiac rate. The two chief cardiac effects of digitalis stimulation of the vagus centre are slowing of cardiac rate and depression of conduction of the cardiac impulse from auricles to ventricles. The other cardiac effects of vagus activity, inhibition of contractility and of irritability may be masked or overcome by the effect of the drug directly on the heart muscle, for they are not observed.

Reduction of the rate of the heart beat was the first digitalis effect to attract attention in experiments on animals, and these observations profoundly influenced the conceptions regarding the therapeutic use of the drug. Digitalis has been used by physicians for many years with the expectation of slowing the heart rate of patients in the same manner in which slowing is produced in animals. It is true that the reduction of the accelerated cardiac rate is without doubt the most important effect of digitalis in heart disease but this valuable effect occurs in a striking manner only in one form of cardiac disturbance, namely, auricular fibrillation, in which digitalis accomplishes the reduction of cardiac rate by an action quite different from that causing the slowing observed in animals and in man with normally beating hearts. This point will be discussed later when the use of the drug in auricular fibrillation is considered, but to avoid confusion, it is necessary to draw the distinction at this time between the action of digitalis on the normally beating heart and on the heart in which the auricles are in a state of fibrillation. It is only when these two conditions are differentiated that reliance can be placed on statements regarding the influence of the therapeutic action of digitalis on the cardiac rate. As it was not possible to determine with certainty the existence of auricular fibrillation before the employment of the electrocardiograph, only the literature of approximately the last ten years can be said to furnish reliable evidence on this point.

The question under discussion here is the ability of digitalis to slow the rate of impulse formation in the normally beating human heart by inhibition through the vagi of the rate of impulse formation.

Divergent opinions have been expressed by various students of digitalis. Wenckebach (155) states that the regularly beating heart is slowed by the action of digitalis on the vagus nerves and compared its action to the effect obtained by stimulation of the vagi by pressure

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over their trunks in the neck. On the other hand, the drug was found to have almost no effect in most cases with normal rhythm in the series carefully studied by Mackenzie (107). He observed occasionally, however, striking slowing of the cardiac rate in cases with normal rhythm following the administration of digitalis, which he thinks is possibly due to the stimulation of the vagus nerves by the drug. Cushny (29) observed slowing of the heart in 6 of 18 patients with normally beating hearts to whom full doses of digitalis were given. The relation of the slowing in the cases in which it does occur due to vagus action was studied later by Cushny, Marris and Silverberg (32). They noted the effect of vagus paralysis by atropin in patients affected by digitalis, and attempted to distinguish between the effects of the drug directly on the heart muscle and those induced through vagus stimulation. They concluded that the effects produced through the vagi do not play any part in the beneficial action of the drug.

Cohn and Fraser (22) have reported repeated observations on the effect of digitalis on twelve patients with normally beating hearts. Daily electrocardiograms were taken and the drug was administered until a disturbance in the rhythm of the heart was effected, at which time the patients usually had gastric symptoms. In regard to the effect of digitalis on the heart rate they say:

> Slowing of the heart, even when the rhythm is normal, is still taken in many quarters as a measure of the efficiency of digitalis. The slowing of the heart which takes place *after* the onset of the symptoms of intoxication can hardly be taken to be of benefit. But before the symptoms occurred, slowing took place in only one patient, and this one was the subject of abrupt fluctuations in rate without the use of drugs. Slowing was observed in five more patients, but not until two days after rather severe symptoms of intoxication had set in. Two of these patients had quite normal hearts, anatomically and functionally. It appears then that if the patients are divided into two groups, those in whom slowing occurs before and those in whom it occurs after the onset of digitalis intoxication, slowing will rarely be observed in the first group—and the slowing which is observed in the second group is an effect which can, in the long run, scarcely be desirable.

In a later publication, Cohn (20) states:

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We have been led to conclude from our observations that digitalis slows the sinus rhythm only in the group of hypodynamic hearts, and that to produce slowing is not a primary function of digitalis in therapeutic doses.

White and Sattler (160) report the effects of large doses of digitalis on ten healthy young adults. The effects of the drug were observed by daily electrocardiograms. Marked slowing occurred in two subjects, the heart rate reaching 43 beats per minute in each instance. In two other subjects, the heart rate became lower than usual at night when under the influence of the drug. In the other six cases, no change in heart rate occurred.

Parkinson (119) administered digitalis in full doses to 20 soldiers with cardiac symptoms, a rapid pulse rate and with normally beating hearts. (Effort syndrome.) He reports that the heart rate was reduced but little, and that the group of patients was scarcely influenced by digitalis. Pratt (122) states that his experience with digitalis confirms the findings of Mackenzie and Cohn and Fraser that digitalis rarely slows the rate of normally beating hearts until toxic symptoms are produced.

Robinson (130) has reported the effects of large single doses of digitalis on a series of approximately one hundred patients, and although striking effects were obtained in cases with auricular fibrillation, practically no change in the heart rate was observed in patients with normally beating hearts to whom the same amounts of digitalis were given.

On the other hand Sutherland (147) reports slowing of the normally beating heart by digitalis. He treated a series of cases of rheumatic heart disease with rapid cardiac rates, usually in children or in young patients. He states that digitalis caused slowing of the cardiac rate practically uniformly and the results in these cases were as definitely good as those usually seen in cases of auricular fibrillation.

McCulloch and Rupe (112a) have quite recently confirmed Sutherland's observations. They studied the effects of the drug on a series of children with heart disease, and found that slowing of the heart-rate of ten or more beats occurred so constantly when full therapeutic doses were given, that this effect could be used as a sign of digitalis action. They recommend the use of the drug in children with heart disease for the purpose of slowing the heart rate when it is more or less

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persistently accelerated, and when such causes of acceleration as pain, fatigue, excitement and fever have been removed.

Pardee (118a) has also observed slowing of the normally beating heart following the administration of large single doses of the tincture. The onset of the slowing in the nine cases studied was noted to occur before the changes in the T wave of the electrocardiogram in three patients. The two effects occurred synchronously in four patients, while the T wave changes occurred first in two. The heart was considered as slowed when the rate was found to be ten beats per minute slower after the drug was given than in several counts before. The size of the single doses was determined by giving 1 minim of a fairly good tincture per pound of body weight.

Certain facts that have been demonstrated by animal experiments seem to show why the reduction of the cardiac rate is not more often seen in patients. Halsey (63) found that the dose which causes slowing and other signs of vague stimulation lay between 30 and 40 per cent of the minimum lethal dose of g-strophanthin, of digipuratum and of a fluid extract of digitalis given intravenously in dilute solutions in about fifteen minutes. Robinson and Wilson (134) slowly administered a diluted tincture of digitalis intravenously into a series of cats and followed the effects of the drug by electrocardiograms. In these experiments, the heart rate was slowed gradually, the effect being first seen with about 25 per cent of the minimum lethal dose, while the maximum slowing occurred when about 70 per cent of the minimum lethal dose had been given. In a second series of cats in which the vagi had been cut, practically no slowing of the heart rate was observed.

It seems evident that the amount of digitalis which is necessary to stimulate the cardio-inhibitory centre sufficiently to cause slowing of the heart-beat is usually greater than the amount that can be given to patients without the production of toxic symptoms. However, individuals whose vagus centres are more easily stimulated than usual or whose hearts are unusually susceptible to the slowing action of the vagi, are exceptions to this rule. Children apparently fall into this category. It is evident that the reduction of the rate of the normally beating heart should no longer be looked upon as an effect which digitalis should be expected to produce at least in adults although such an effect is desirable in many cases, of heart disease.

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c. The effect on conduction. The depression of the conduction of the cardiac impulse between the auricles and ventricles has already been discussed briefly as a toxic manifestation of digitalis. As this effect plays an important part in the therapeutic action of the drug, and as it is at least in part brought about through the cardio-inhibitory mechanism, it deserves further consideration at this point.

The experimental studies of von Tabora (148) drew attention to the fact that digitalis depresses conduction through its action on the cardio-inhibitory centre. He concluded that this effect is produced both through the vagi and by the direct action of the drug on the conducting pathway. He also showed that digitalis is more effectual in animals when the A-V bundle had been injured.

Although the clinical recognition of the influence of digitalis on conduction has been general since it was first pointed out in patients by Mackenzie (106) there has been a discussion as to whether it should be regarded mainly as an effect of vagus stimulation or as an effect produced by the direct action of the drug on the heart.

Although the general opinion seems to favor the idea that vagus stimulation is largely responsible for the effects of digitalis on conduction, Cushny, Marris and Silverberg (32) concluded from their study of this problem on patients that the cardio-inhibitory mechanism is of minor importance, and they emphasize the direct action of digitalis on the heart. Cushny (31) expresses the opinion in a later publication, however, that digitalis may effect conduction by either method, and the condition of the heart is the factor determining which of the two methods will predominate. He seems to believe that in normal hearts the conduction is depressed through the inhibitory mechanism; while in diseased hearts, where conduction is already damaged, heart-block or delayed conduction is caused by the direct action of the drug.

Wedd (152) who studied the effect of atropin after full doses of digitalis in a large series of cases, concludes that in all cases the action of digitalis is both central, in the medulla, and local, in the myocardium. He observed that in 100 per cent of his cases of auricular fibrillation, and in 76 per cent of those with normal mechanism, the heart rate failed to return after atropin injections, to the level at which it was before being slowed by digitalis. He believes that it is

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possible to measure the local action of the drug by the degree which atropin fails to restore the heart to its original rate. Wedd considers that Cushny has perhaps gone too far in ignoring the action of digitalis on the cardio-inhibitory centre in certain types of heart disease, in which the local action on conduction seems to predominate.

The observations of Cohn and Fraser (22) show clearly the manner by which digitalis affects the conduction of normally beating hearts when presumably not extensively damaged by disease. The twelve patients to whom digitalis was given until symptoms of intoxication appeared, were studied by means of electrocardiograms. In all but one, conduction was affected by the drug, as evidenced by lengthened conduction time or by blocked auricular impulses. The administration of atropin by subcutaneous injections caused the conduction to return practically to its normal condition, in all cases, regardless of the degree of depression that had been present. It is evident therefore that in these cases the effect on conduction was entirely produced by stimulation of the cardio-inhibitory mechanism, as it was abolished with vagus paralysis. The interesting observation was also made that the rate of the heart when reduced was not restored by atropin in a manner that paralleled the restoration of conduction.

White and Sattler (160) confirmed these observations in ten healthy young adults. They found that atropin completely removed the effect of digitalis on auriculo-ventricular conduction, and they concluded that the effect on conduction was almost entirely, if not entirely due to increase of vagal tone and irritability.

The foregoing observations demonstrate that the conducting system is capable of being effected by digitalis when the heart is presumably normal. However, depression of conduction does not become marked until large doses are given. Cohn (20) has observed delayed conduction forty-eight hours after the administration of the drug was begun, and in many instances, the conduction time gradually lengthened during the succeeding three to five days until partial block occurred. Heart block may occur, however, with extreme abruptness within a few hours. In the healthy young subjects studied by White and Sattler (160) the first effects on conduction were seen after 1.5 to 1.8 grams of the leaf had been administered; but there was no marked prolongation of the conduction time until 2.7 grams had been

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taken. This latter dose is about that which, on an average, produces toxic symptoms.

There is no doubt that in heart disease when the tissues of the conducting pathway are damaged, digitalis heart-block may be produced by much smaller doses of the drug than those producing it in normal hearts, but it can no longer be said that digitalis produces heart-block only in hearts in which the conducting mechanism is already damaged. The problem of the conduction effects of digitalis in heart disease is a complicated one, and considerable light is still needed on this subject for its complete understanding.

Depression of conduction may be an important factor in the beneficial effects of digitalis in two ways. In the first place, it prevents the improper stimulation of the ventricles by the auricles. As will be seen when auricular fibrillation is discussed, the ability of digitalis to prevent stimuli from reaching the ventricles is of paramount importance in the treatment of certain forms of heart disease. In the second place, depression of conduction allows a longer period to elapse between auricular and ventricular systole, and Cohn and Fraser (22) have suggested that this may be a matter of some importance in the treatment of patients who have mitral stenosis. They point out that in these patients,

> the initial and most important of the factors which tend to disturb the circulation is the narrow auriculo-ventricular orifice, which prevents the complete empyting of the left auricle within the time allowed before the ventricles contract. If one could lengthen the conduction time and could keep it lengthened, thus separating the contractions of the auricles and ventricles as widely as possible, much aid could be given patients of this class in maintaining a satisfactory circulation. There is reason to believe that this can be done.

3. The effects on the blood vessels

a. The effect on blood pressure. Cushny (28) states that Blake discovered in 1839 that digitalis caused an elevation of blood pressure in experimental animals. From that time until quite recently, this effect and the effect on the heart rate have almost predominated the field of digitalis action. It was generally believed that the arterial pressure was raised by increased force of the ventricular contractions

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and by the constriction of the blood vessels. It is an interesting fact that neither of these effects has been demonstrated in man as a direct action of the drug, although there is indirect evidence that the first of these effects occurs, as was pointed out, when the action of digitalis on the heart muscle was considered. The effect of digitalis on the blood pressure is of such importance that it is desirable to consider briefly some of the experimental work bearing on this subject before reviewing the more recent clinical studies.

The chief exponents of the idea that digitalis has a direct action on the blood vessels have been Gottlieb and the members of his school. Numerous investigations have been reported from his laboratory bearing on this subject.

The most important study to lead to the belief that the digitalis bodies are capable of producing marked vascular constriction through direct action on the vessel walls has been, according to Eggleston (43) that of Gottlieb and Magnus, published in 1902. By the use of doses of various digitalis bodies which were five to fifteen times the minimum lethal dose, they produced striking elevation of blood pressure in experimental animals, which was in part caused by constriction of the splanchnic vessels by direct action of the drug upon their walls.

Among other publications from Gottlieb's laboratory which are of interest, several may be mentioned. Kasztan (87) in 1910 showed that when Ringer's solution containing not more than 0.05 mgm. of crystalline strophanthin to 100 cc. was perfused through the kidneys of dogs, cats and rabbits, arterial dilatation took place; while if the solution contained 0.1 mgm. of strophanthin, arterial constriction occurred. The weaker solution when perfused through the intestinal vessels, however, caused them to constrict. This work was confirmatory of that of Jonescu and Loewi (85), who considered that dilatation of the renal vessels occurred as a direct peripheral effect on the vessels. Fahrenkamp (51) repeated the work of Kasztan, using, however, digitoxin instead of strophanthin. He obtained an effect on the renal and intestinal vessels, similar to that observed by Kasztan. He found further that concentrations of digitoxin which contracted the kidney and intestinal arteries had no effect on the vessels of the skin and muscles. Cats and rabbits were used, and Fahrenkamp found that 0.7 mgm. of digitoxin per 100 cc. Ringer's solution caused dilatation

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of the renal vessels of the cat; that 0.48 mgm. produced the same effects in rabbits, and that 1.2 mgm. of digitoxin caused contraction of these vessels in both animals.

Later Joseph (86) investigated a similar subject in Gottlieb's laboratory and studied simultaneously the effect of small doses of strophanthin and digitalis (digipuratum) on the heart and on the vessels. He attempted to use doses comparable to those employed in the therapeutic use of these drugs; but, as a matter of fact, his doses appear to be considerably larger as a rule. He found that in rabbits and cats the action of these drugs on the heart and on the vessels are not synchronous and that they seem therefore to be independent. Digitalis was found to cause at first a dilatation and then a constriction of the vessels, which in the intestines, outlasted all other effects. The kidney vessels dilate while the intestinal vessels contract. Joseph considers that he succeeded in demonstrating vascular effects with any dose that affected the heart. The slowly developing and persistent narrowing of the intestinal vessels is the most frequent and most striking digitalis effect which he observed.

Gottlieb (59) has laid great stress on these and similar investigations. He holds the view that the power of digitalis to alter the size of important vascular systems is of prime importance, and that the alteration of the distribution of the blood which digitalis causes is the main factor in its curative action. He believes also that the vascular changes caused by digitalis are, in large measure, responsible for an elevation of the blood pressure in man when the drug is given in therapeutic doses.

Krehl (90) has also recently stated that he considered the best results from the use of digitalis were obtained in patients in which there is altered blood distribution.

Eggleston (43) has recently published a critical review of the investigations of the Gottlieb school and has commented upon their bearing on the question of *blood pressure* changes caused by digitalis in man. He points out especially the great divergence in dosage under the two conditions and says

> it must be quite obvious to anyone who gives the matter a moment's thought that it is utterly fallacious to reason from such experiments that similar effects would be produced in man from the therapeutic use of digitalis or its congeners.

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The discovery that elevation of blood pressure is not a constant or conspicuous effect of digitalis in man occurred when the sphygmomanometer was introduced into clinical medicine, and when accurate objective observation began to replace deductions from animals and observations strongly influenced by preconceived ideas. In 1901 Sahli (quoted by Eggleston) stated that in cases with circulatory stasis and high blood pressure, digitalis not only relieved the stasis, but also very often reduced the blood pressure by from 30 to 40 mm. of mercury. The findings of Sahli have been amply confirmed by such careful students of the effects of digitalis on man as Mackenzie (108), Cushny (29) and Cohn (21). Eggleston (43) has summarized the findings of a number of observers[1] who have studied the effect of digitalis on blood pressure. He says:

We find that the systolic blood pressure was recorded for 181 cases. In 66 of these, or about 36 per cent, the systolic pressure is stated to have risen or to have tended to rise; in 57 or 31 per cent, it fell; and in 58, or 32 per cent, it is recorded as having shown no change. In 116 instances in which the diastolic pressure is mentioned, it is stated to have been increased in 24, or 15 per cent; and to have fallen in 76 or 65 per cent. While the actual extent of the changes is not always stated, it would seem that digitalis is about as likely to influence the systolic pressure in one direction as in another, or not to alter it at all. With the diastolic pressure, however, the chances are nearly two to one that digitalis will cause some reduction, and the chances are more than three to one in favor of its reducing it as compared with the likelihood of its raising it. Other things being equal, this evidence certainly does not point to the occurrence of any marked vasoconstrictor action of the drug in man. The opinions expressed by the several authorities cited are in very general agreement that digitalis has little constant influence on the systolic blood-pressure when used therapeutically, and some even go so far as to suggest that it actually often causes some vasodilatation which would account for the reductions observed in the diastolic pressure.

Eggleston's own observations have been perhaps the most valuable contribution to the study of the influence of digitalis on blood pressure

[1] The work here summarized is that of Czyhlarz, Gross, Neu, Geisböck, Schwartz, Fellner, Szinnyei, Price, Lawrence and Cadbury. References to their papers are given by Eggleston.

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in man. The various conditions of the study were carefully controlled. An assayed extract of digitalis or digitoxin in the form of tablet triturates or of the granules of Nativelle's digitaline crystalisée were given in large doses. The full amount calculated, according to body weight, was administered in twelve or eighteen hours and the effects of the drug on the heart were followed by polygraphic and electrocardiographic methods. The blood pressure was recorded for three days before and three days after the drug was given. Eggleston's series consist of 14 patients, 6 of whom had high initial pressure while 8 had normal or low initial pressure. His study revealed the fact that

> the administration of large doses of digitalis or digitoxin has very little tendency to elevate the systolic pressure, this having been increased by 11 mm. of mercury in one, and 15 mm. in a second case. In only one case was the systolic pressure materially reduced, namely by 23 mm. of mercury. On the other hand, the diastolic pressure was significantly lowered in 7, or 50 per cent of the cases, while it was never significantly raised.
>
> It is evident, therefore, that digitalis and digitoxin have very little influence on the systolic pressure in either direction, that they tend to produce a significant reduction in the diastolic and more decidedly, to produce a material increase in the pulse pressure.

Eggleston found that alteration in the pulse rate did not offer an explanation for the changes occurring in the diastolic pressure. The facts brought out by this study abundantly warrant the conclusion that "there is no evidence that either digitalis or digitoxin has any direct action on the vessels when given to man even in large therapeutic doses."

Eggleston's observations show that the net changes in the systolic, diastolic and pulse pressure differ in different cases in order best to meet the condition prevailing, and they indicate that studies on the blood pressure effects of digitalis must always take into strict account the condition of the patients under observation.

It will no doubt be some time before clinicians generally learn that arterial hypertension does not contraindicate the use of digitalis, but may in fact be advantageously affected by its action. However, clinicians have reported favorable results from the drug in cases with elevated blood pressure. Windle (162) has recently stated that

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digitalis is valuable to patients with degenerated arteries, high blood pressure and anginal symptoms and may bring about an immunity from angina. Lawrence (91) has expressed similar views after a careful study of the blood pressure in 26 cases, during treatment with digitalis. Danielopolu (34) treated 36 cases of arterial hypertension with Nativelle's digitaline, although he remarks that the work dealing with the action of digitalis on the arteries made him hesitate to do so. His patients had arterial sclerosis and nephritis. Of the 36 patients a fall in the systolic pressure occurred in 19, while in 24 patients, the diastolic pressure was reduced: In 2 patients, a fall in systolic pressure alone was observed. The reduction of the arterial pressure amounted to 10, 20 or even 30 mm. of mercury.

During a study of one hundred patients, some of whom had hypertension, to whom very large single doses of the tincture of digitalis were given, Robinson (130) noted that the systolic pressure tended to approach more nearly the normal level after the drug was given. In other words, elevated blood pressure fell, while abnormally low pressure rose after the drug was given. These observations confirm Eggleston's more detailed study.

It is by no means desirable that the state of the blood pressure should be no longer taken into consideration in determining the indications for the use of digitalis or in studying its effects in man. Recent experimental observations by Cohn and Levy (26) indicate that under conditions kept as nearly similar as possible to those pertaining in the clinical use of digitalis, the blood pressure of dogs may be elevated by g-strophanthin and the tincture of digitalis. During a study of the effects of therapeutic doses of digitalis on the contraction of the heart muscle, they studied the blood pressure of normal dogs when not under operative conditions by the method of van Leersum, and noted the effect of the drugs used when given in doses on the same body weight basis as used in patients, which produced no evidence of severe intoxication. In the few animals thus studied, they found that the blood pressure usually rose, the increase varying from 20 to 66 mm. of mercury.

Cohn and Levy seem to attribute the rise of blood pressure which was transient, to the effect of the drugs on the contraction of the heart muscle.

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It is not possible to dismiss the subject of the effect of digitalis on blood pressure as non-existing, but the older ideas must give place to those resting upon the accurate clinical studies that have been made since the introduction of the sphygmomanometer, and arterial hypertension must not be accepted as a reason *per se* for withholding digitalis when it is otherwise indicated.

b. The effect on the coronary circulation is a subject about which there has been a certain amount of speculation and which has also been studied experimentally. Although theoretically it is of much interest, practically, no facts have been established which bear directly on changes in the coronary arteries with therapeutic doses of the drug, and no definite information regarding the effect of digitalis on the coronary circulation of man has been obtained.

Eggleston (47) has recently reviewed this subject. He points out that it assumes some importance because of statements that appear in some recent textbooks to the effect that digitalis may cause a dangerous constriction of the coronaries, and is therefore contraindicated in angina pectoris. There seems to be no evidence for the idea that digitalis causes coronary constriction. The experiments of Felix Meyer and of Sakai and Saneyoshi (quoted by Eggleston) have shown that the coronaries do not contract under the influence of digitalis but if they are affected at all, they probably dilate. Bond (10) investigated the influence of digitalis and strophanthus on the coronary blood flow of dogs, measuring the coronary flow by the number of drops in a given interval of time coming from the coronary veins. He could find no effect attributable to these drugs, and concluded that the coronary blood flow is probably regulated by the systemic blood pressure, as it was decreased when the blood pressure was lowered by nitroglycerin and amyl nitrate.

Voegtlin and Macht (150a) investigated the action of a number of drugs of the digitalis group on strips of mammalian coronary arteries. They found that digitoxin, crystallized German digitalin of Merk and bufagin especially caused coronary constriction under the conditions of their experiments, while digitonin and preparations containing this saponin-like body caused relaxation. Strophanthin was found to be practically inert in this respect. Voegtlin and Macht think that these observations have considerable importance in the therapeutic use of

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digitalis especially in the treatment of angina pectoris, when they believe a nitrite which they find causes coronary relaxation should be combined with the digitalis.

Eggleston (47) also discusses the relation of the blood supply to the heart muscle through the coronaries to pulsus alternans, and expresses the opinion that although this derangement of the heart may occur apparently as a result of digitalis, this is no reason for considering that digitalis brings on this derangement by coronary constriction. Pulsus alternans may also disappear when digitalis is given.

It is safe, therefore, to say that at present there is no reason to believe that the digitalis bodies affect the blood flow through the coronary arteries by direct action on these vessels.

c. The effect on the venous blood pressure in man has been studied by Capps and Matthews (11), who used both digitalis and strophanthin, and obtained no evidence of changes in the venous pressure.

4. The effects on the kidneys

The use of digitalis as a diuretic begins with its introduction into medical practice in 1785, as Withering (163) recommended it especially for the removal of dropsy and emphasized its action on the kidneys rather than its action on the heart. Withering mentions diuresis as one of the cardinal effects of digitalis, and recommends that its occurrence should be taken as an indication for discontinuing its administration.

The manner in which digitalis causes diuresis has been one of the controversial points regarding the action of the drug. The chief discussion has arisen over the question as to whether diuresis is in reality a direct effect of the drug on the kidney and its vessels, or whether it is secondary to an improved state of the general circulation. Various opinions are held regarding this point.

The experimental studies of Gottlieb and Magnus, Jonescu and Loewi (85), Kasztan (87), Fahrenkamp (51), and Joseph (86) have already been referred to in discussing the action of digitalis on the blood vessels. The fact that dilatation of the renal vessels is caused by weak solutions of the digitalis bodies cannot, as it was previously pointed out, be taken as evidence from which conclusions can be drawn regarding the effects of therapeutic doses of the drug in man.

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The conditions are far from comparable. On the other hand, these experiments clearly indicate that the kidney vessels differ in their reaction to digitalis from other vessels, especially those of the splanchnic area. This fact is inviting as a basis upon which to build a theory of digitalis diuresis, as Gottlieb and others have done. Generally speaking, the ground is considered insecure, and the results of clinical studies show that the diuretic effects of digitalis do not occur as they would were the theory of Gottlieb correct. The quantitative study of diuresis has recently been much improved by the organization in hospitals of means of accurately measuring the intake and output of fluids of patients and accurate records of body weight.

Since the introduction of such methods, Mackenzie (108) has reported that diuresis is not very evident in patients even when digitalis is given to the stage of toxic symptoms, and he considers that no definite conclusions are justified regarding diuresis from his careful study of the action of digitalis. Cushny (29) observed diuresis only in patients in whom dropsy was present, and Agassiz (2) obtained similar results from the intravenous administration of rather small doses of strophanthin in cases of auricular fibrillation. Diuresis occurred only in the presence of edema. Cohn (20) has also emphasized this distinction, and reports that in the group of patients which he studied with much care, diuresis was never seen in patients without edema. He concludes from his experience that a specific effect on the urinary output does not occur as the result of giving digitalis to patients with normally beating hearts without the presence of edema. Cohn (21) has also found that diuresis is usually marked when edema is present. Christian (16) in emphasizing the beneficial effects which may be obtained from digitalis in chronic cardiac cases with edema in whom there was no irregularity of the pulse, points out the striking diuresis and loss of body weight which may occur in these patients, and publishes a series of charts illustrating his results. There seems to be in his cases a relation between the amount of edema and the extent of diuresis. The reports of other observers tend to confirm these findings. It is evident that some factors other than dilatation of the renal vessels take part in the increased flow of urine produced by digitalis. The question of the effect of digitalis on water exchange has been recently discussed

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by Krehl (90) who is no doubt more or less influenced by the views of his colleague, Gottlieb.

The question of the action of digitalis on the kidneys has been investigated by Reinike (124) by an experimental method differing from those already mentioned. Digitalis was administered over a long period of time to rabbits, and was found to cause an enlargement of the kidneys as compared with those of control animals. This suggested that the kidneys had undergone excessive activity under the influence of the drug. No definite conclusions, however, are justified from Reinike's experiment, as the drug was given to only four animals, and they did not show uniform results.

In spite of the fact that there is nothing definite on which to base a claim that digitalis produces diuresis by direct action on the kidneys, the position that the kidneys play no part in digitalis diuresis, does not seem to be entirely justified. However, several pharmacologists who have been especially interested in the action of the drug state that diuresis is entirely a secondary effect.

Hatcher (70) says:

> None of the drugs of this group are actively diuretic through any direct action on the kidneys. They induce diuresis solely through an improved circulation. That does not mean either a higher or a lower blood presure in every case; it means a more effective circulation, one better adapted to the needs of the individual patient. This sometimes means an increase, sometimes a decrease, in pressure.

Sollmann (143) holds a similar opinion regarding the diuretic action of the drug.

In Eggleston's (47) most recent paper on digitalis, he says:

> While it has been claimed that digitalis exerts a specific diuretic action on the kidneys, or that it produces diuresis by selective vasodilatation of the renal arterioles, the evidence for these claims is quite unsatisfactory, and careful studies have shown conclusively that the drug is not a diuretic in normal animals. It has also been observed repeatedly that no diuresis follows the administration of digitalis to normal human beings or to those with heart failure uncomplicated with edema or serous effusions. In cases of nephritis with edema, or even with general anasarca, digitalis also produces no diuresis when heart failure is not associated with the nephritis.

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When, however, heart failure is accompanied with edema or anasarca, profuse diuresis may follow the administration of digitalis, but this is found to occur only when the heart failure is more or less effectively overcome by the drug, and when the heart failure is not affected, no diuresis ensues from its administration. It is clear, then, that the diuretic action of digitalis in man, is essentially secondary to its capacity to relieve heart failure and restore the circulation; and when it is effective in edematous cases of heart failure, it is often one of the earliest of the manifestations of the action of the drug, though other evidences can be detected if looked for. When adequate digitalization fails to produce diuresis in a patient with edema and heart failure, it will almost invariably be found that either the heart failure has not been relieved or that the failure is complicated by nephritis, which then demands appropriate treatment.

At variance with Eggleston's idea regarding the relation of nephritis to digitalis diuresis are the findings of Hedinger (quoted by Edens, 37) that digitalis has a direct diuretic action on the diseased kidney, which is independent of its action on the heart. However, there is considerable chance for differences of opinion as to what is meant by a diseased kidney.

The idea that pathological changes may influence the effect of digitalis on the kidneys appears again in a recent paper by Jarisch (84). He reports two cases of syphilitic aortitis in which diuresis was inhibited by therapeutic doses of digitalis but was increased by very small doses. Jarisch makes use of an idea of Meyer (113) in order to explain these results that increased excitability of the renal vessels lowers the threshold for both the vasoconstricting and vasodilating action of digitalis. He suggests that both patients had increased excitability of their renal vessels as the result of the incipient stage of contracted kidneys that was present. He states that his findings are in accord with those of Meyer who found that in early nephritis diuresis was produced by smaller doses than when the kidneys were normal. Jarisch considers that small doses of digitalis should be used when nephritis is present, and that caution as to dosage should be used in heart cases that have low specific gravity of the urine, which points to renal sclerosis.

The relation of the output of urine and alterations in blood pressure has been studied by Lawrence (91) who found that in his 26 patients,

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diuresis was always accompanied by a fall in blood pressure, and 88 per cent of the cases showing a fall of blood pressure had diuresis. These findings, although of interest, do not, at present, add evidence of value in determining the manner of production of diuresis by digitalis.

The question as to a primary or direct action of digitalis on the kidneys or its vessels in cases of cardiac failure with edema, should be considered as yet unsettled, although it has been abundantly demonstrated that digitalis has no diuretic action except under very special conditions.

Cohn (20) has reported that a diminution in the output of urine is sometimes seen when well marked toxic symptoms appear. This phenomenon is adequately accounted for, he believes, by the presence of nausea and vomiting, which diminishes the fluid intake and may result in the loss of considerable fluid by emesis. This observation is confirmatory of a statement by Withering who said that large doses of digitalis may check the flow when smaller doses had increased it.

IX. THE USE OF DIGITALIS IN HEART FAILURE

Digitalis has attained the reputation of being the most valuable drug in the treatment of heart disease, and by the term heart disease is usually meant a group of symptoms such as dyspnea, cough, chest pain, edema, cyanosis, weakness, and palpitation. These symptoms are in reality not evidence of heart disease, but of heart failure, and they occur as a group only when the heart is unable to maintain the normal circulation of the blood. Heart failure may result from a variety of cardiac disorders; some of which are much more susceptible to a favorable influence by digitalis than others. The great reputation of the drug in heart disease doubtless rests upon the striking benefits which it produces in cases of heart failure dependent upon one particular type of cardiac derangement. On the other hand, fault has been found with the drug when it has been used in heart failure dependent upon other causes with the expectation that similar results are to be obtained. In considering the therapeutic use of digitalis, it is just as necessary to take into account the various cardiac derangements responsible for heart failure as it is the effects produced by the drug.

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In fact, it is only when these two aspects of the subject are brought together that a rational basis for the therapeutic use of the digitalis bodies can be established. It is undoubtedly because clinicians have not fully understood the action of digitalis and because pharmacologists have not fully understood heart failure, that so many misconceptions have existed in the past regarding the therapeutic use of digitalis. The coöperation of clinicians and pharmacologists which has recently come about has been responsible for some of the most valuable contributions to the present-day knowledge of digitalis. Examples of this coöperation and collaboration are those of Mackenzie and Cushny in England and of Eggleston and Hatcher in America. This type of coöperative work is greatly to be desired, and is destined to bring forth results of great value in many fields of medicine.

1. Classification of heart failure

In the following part of this review, the relative value of digitalis will be discussed in the various disorders of the heart which are commonly seen; and which may lead to the failure of that essential organ to maintain an efficient circulation of the blood. Cohn (20) has emphasized the desirability of considering the action of digitalis in its relation to various forms of heart failure, which he has divided for this purpose according to the following table.

A. Normal rhythm.....	a. Without edema	1.	With normal blood pressure
		2.	With high blood pressure
	b. With edema	3.	With normal blood pressure
		4.	With high blood pressure
B. Auricular fibrillation ..	a. Without edema	5.	With normal blood pressure
		6.	With high blood pressure
	b. With edema	7.	With normal blood pressure
		8.	With high blood pressure

This classification shows the importance Cohn has placed upon the type of cardiac rhythm, the presence of edema and the state of the blood pressure in the reaction of the heart and circulation to digitalis. He has discussed his observations on the action of the drug in patients with normal cardiac rhythm, without edema and with normal blood

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pressure; and a comparison of the action of the drug in these patients with those in other groups has led him to conclude as follows:

It seems important to emphasize the fact that it is essential to distinguish differences which patients suffering from heart disease present and to study them in groups, with these differences in mind. Rhythm certainly offers a prime basis. The effect of digitalis on rate and on a number of other capacities varies with the nature of the disturbed function.

In actual practice, it is often impossible to classify sharply cases of heart failure on the basis of the derangements of function underlying their production. Nearly every case results from a combination of causes, and these causes must be evaluated relatively to one another, in any attempt to arrive at a clear understanding by which treatment may be intelligently instituted. The ability to determine the relative importance of the various factors underlying the production of heart failure is an essential requirement for its successful treatment. The disorder of the heart revealed most prominently by all the means of examination now available may often be unimportant or only contributory in the production of heart failure in any particular case. The relative importance of valvular and muscular lesions of the heart may be cited as an example. In many cases, a valvular defect obtrudes itself upon the physician, while muscular inefficiency, so difficult or impossible to determine directly, is in reality the actual cause of heart failure. It is necessary to point out the difficulties regarding the classification of heart failure on the basis of its causation, because a discussion of the effects of digitalis in this relation to the various disorders of the heart cannot take into account many of the practical problems involved in the use of the drug in the treatment of heart failure. These can only be solved by the careful study of patients, in whom a great variety of conditions and circumstances are encountered, calling forth constantly the exercise of clinical judgment, which cannot be acquired from books, but only at the bedside or in the consulting room.

2. Disturbed cardiac mechanism

a. Auricular fibrillation. Following the suggestion of Cohn, rhythm is taken as a prime basis for distinguishing the various types of

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disorders of the heart, and those disorders associated with or consisting of disturbed cardiac mechanism will be considered before those with normal mechanism and regular beating hearts are taken up. It seems desirable to adopt this order and to discuss first the use of digitalis in auricular fibrillation, because it is in this type of deranged cardiac rhythm that digitalis produces its most brilliant results, a point which it is well to emphasize at the outset.

A clear understanding of auricular fibrillation is essential for the intelligent employment of digitalis. It has been especially well described by Lewis (100, 101), to whose work the reader is referred.

The salient features by which this condition is recognized may be summarized as follows: The pulse and the cardiac sounds occur irregularly without any order to the arrhythmia, and usually with a considerable increase in rate. There is no evidence of the normal auricular contractions in the veins of the neck, as shown by polygrams, and the auricular waves, the so called P waves, of the electrocardiogram disappear. A constant succession of small waves may sometimes be seen in the venous pulse curve, while the electrocardiogram shows almost constantly a series of small rapidly recurring waves, lacking uniformity and well defined form, seen throughout the diastolic portion of the curve. All these phenomena are readily appreciated when it is realized that the auricles no longer contract as a whole in a rhythmical fashion, but stand in diastole with their separate fibers contracting and relaxing one after another constantly. This abnormal type of auricular action sends down impulses to the ventricles more frequently than the normally beating auricles and the rhythmical character of the impulse formation is lost. A rapid irregular ventricular action therefore results which is distinctly less efficient in the maintenance of the circulation than is the slower regular normal beat. This increase in rate is often an important factor in the failure of the heart when auricular fibrillation is present.

Auricular fibrillation was recognized as a common disturbance of the human heart-beat in 1909, when Rothberger and Winterberg and Lewis simultaneously demonstrated its existence by means of electrocardiograms. Several years previously, however, Mackenzie (108) drew attention to the fact that there were striking differences in the effects of digitalis in cases with irregular heart action and in cases

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with regular rhythm, and he stated that "no rational idea of the manner in which digitalis acts can be obtained unless this change in the heart's action is appreciated." He was also perhaps the first to study the effect of digitalis in patients with auricular fibrillation after this condition became established as a clinical entity. His paper which appeared in 1911 was followed shortly by important contributions by Cushny (29) and Edens (37) and, since that time, the value of digitalis in this condition has been generally recognized. It is scarcely necessary to review the papers of other students of this subject, such as Fahrenkamp (52), Fulton (56), Christian (14), Robinson (128), Weil (153), Cohn (20), Borultau and Stadelmann (7), Pratt (122), Wedd (152) and others who have all borne witness to the striking benefits obtained by the use of digitalis in auricular fibrillation. Their papers are referred to in regard to special phases of this subject.

It has been repeatedly shown that the great value of digitalis in auricular fibrillation lies in the fact that the drug slows the abnormally rapid and irregularly beating ventricles, and this effect of the drug is generally considered its most important accomplishment. Lewis (99) has recently expressed what is perhaps an extreme view of this matter. He says:

> The chief value of digitalis lies in the power to control the ventricular rate when fibrillation of the auricles has come. In most patients in whom this disorder of the heart is discerned, the ventricles beat rapidly, at rates of 120, 140, 160 and even more per minute. It is this rapid action which fatigues the heart, and digitalis, by lessening the rate, lessens the fatigue. The normal heart rate, while the body is at rest—to take approximate and convenient numbers—is 60 beats to the minute. Each ventricular cycle lasts one second; of this, one-third is occupied by systole; two-thirds by the resting period of diastole. The heart works one shift and sleeps for two. But if the rate is 120 beats to the minute, then each cycle lasts half a second; systole lasts quarter of a second and so does diastole. Work and rest alternate in equal shifts. As the rate of beating rises, so is systole increased relatively at the expense of diastole. Very important is it, therefore, to reduce the heart rate when this is excessive. A chief cause of rapid heart action when heart failure threatens or has come, is fibrillation of the auricles, and it is in this condition that digitalis acts so beneficially; it reduces and holds the rate within normal bounds.

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The reduction of accelerated ventricular rate is the only important action of the drug upon the human heart of which we have knowledge. There are few, if any, instances, of which we know with certainty, in which digitalis acts beneficially, except cases of accelerated action; there are few instances of acceleration in which the drug produces unquestionable benefit apart from those provoked by fibrillation of the auricles.

The principle of digitalis therapy—and when I speak of digitalis, I include the allied drugs, strophanthus and squills—is that, administered to suitable cases, the heart, by means of it, obtains rest. The giving of this drug to unselected cardiac cases is much to be deplored. Those who regard digitalis as a cardiac stimulant mistake its character; its chief action is to rest the heart. To the heart, foxglove is not tonic, but powerfully hypnotic. It controls the diastoles of the heart; it extends the period of sleep.

Although most students of digitalis do not share entirely the idea of Lewis regarding the relative uselessness of the drug in conditions other than auricular fibrillation, he has well expressed the consensus of opinion regarding its use in auricular fibrillation.

Agassiz (2) has treated a series of cases of auricular fibrillation with small doses of strophanthin administered intravenously and has shown that this drug has a very similar action to that of other members of the digitalis group when employed upon cases of auricular fibrillation. He states that it is a powerful and serviceable remedy when a rapid reduction of the heart rate is desired in cases of auricular fibrillation in young subjects or in those cases which give a history of rheumatism. The heart rate may be reduced from 180 or 160 to 100 or 80 per minute within six or eight hours. Agassiz's method of administration of strophanthin will be taken up later.

As stated previously, the slowing of the heart is brought about by a different mechanism than that by which digitalis slows the normally beating heart. When the auricles are fibrillating, stimuli are sent down to the ventricles unrhythmically and at a rate much higher than from the normally beating auricles. Digitalis depresses the conductivity of the pathway between the auricles and the ventricles, which then allows fewer stimuli to pass. In this way, the rate of the ventricles is slowed and the arrhythmia reduced. This effect is very desirable because the rapid irregular ventricular activity which

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the fibrillating auricles engender is much less competent to maintain the circulation than the ventricular activity of normally beating heart. The ventricles become more competent when they are slowed and regulated by digitalis. The tumultuous action of the fibrillating auricles is not appreciably affected by digitalis as revealed by electrocardiograms. The manner in which digitalis affects the conduction of the cardiac impulse has been already considered.

The question has been raised whether other factors may not enter into the slowing of the ventricles which digitalis produces in hearts with auricular fibrillation, which are not involved in the depression of conduction in the normally beating heart. Cushny has been especially interested in this subject, and has raised the question as to whether the action of digitalis on the cardio-inhibitory centre is the important factor in slowing the ventricles in auricular fibrillation. Cushny, Marris and Silverberg (32) found that the ventricular rate, slowed by digitalis, was not restored to its original rate when the vagi were paralyzed by atropin. They came to the conclusion that in auricular fibrillation, the ventricular slowing was accomplished by other means than by stimulation of the cardio-inhibitory mechanism, which seemed to play no part in the action of digitalis in auricular fibrillation.

They believe that the conductive pathway from auricles to ventricles becomes less excitable when the nutritional condition of the tissues is improved, and that this improvement may result not only from the increased efficiency of the circulation brought about by the direct action of digitalis on the ventricular muscle, but also by lessening the demands on the heart by rest. They explain in this way the ventricular slowing which occurs when patients with auricular fibrillation are put to bed. Their hypothesis calls for the existence of abnormally increased conductivity in the hearts of patients with auricular fibrillation caused by malnutrition of the tissues. This idea is hard to accept in the light of the state of conduction in other types of heart disease in which it can be accurately determined, and is not infrequently found to be decreased.

In a later publication, Cushny (31) gives the results of further work on this subject in which he attempted to reproduce the cardiac condition of cases of auricular fibrillation in perfused hearts. He states

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his belief in two independent reactions of conduction to therapeutic doses of digitalis. The first is that observed in the normal heart of experimental animals and in the normally beating human heart. It is the result of stimulation of the cardio-inhibitory centre.

The second is that observed in cases of auricular fibrillation in man, and results from the direct action of the drug on the conducting system. Cushny believes that the ventricular slowing which digitalis produces in cases of auricular fibrillation is independent of the action of the drug on the inhibitory mechanism, for it is not prevented by atropin. The primary reason why digitalis acts directly on the conducting mechanism in these cases is the malnutrition of the heart and auricular fibrillation merely favors its appearance by accentuating the fundamental cardiac malnutrition. Wedd (152) has also studied a number of cases of auricular fibrillation and has injected atropin during thorough digitalization. He has come to the conclusion that in all cases digitalis affects conduction both by its stimulation of the cardio-inhibitory centre and by its direct action on the heart, with relatively greater local action in auricular fibrillation. Exception is taken to the statement of Cushny that in fibrillation there is no digitalis action through the inhibitory mechanism. Eggleston (47) has recently discussed Cushny's experiments and conclusions and is in substantial agreement with Wedd.

It is well known that some cases of auricular fibrillation are unusually susceptible to digitalis. Robinson and Draper (132) have shown that in cases of auricular fibrillation prolonged stoppage of the ventricles may be brought about by pressure over one of the vagi of the neck. Weil (154) has also found vagus pressure more effectual in auricular fibrillation than in other conditions, a result which he attributes to an impaired state of the heart. He also found that the normally beating hearts of patients to whom digitalis had been given were more apt to respond to vagus pressure by depression of conduction than were the hearts of untreated patients. Weil believes that digitalis stimulates the cardio-inhibitory centre and, at the same time, renders the conducting system more susceptible to the influence of the vagi. Fahrenkamp (52) found that in cases of auricular fibrillation pressure over the vagus nerves was sometimes effectual in stopping the ventricles after the administration of digitalis in cases in which

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vagus pressure was ineffectual before the drug was given. These findings suggest that the conduction mechanism is rendered more susceptible to vagus action by digitalis, which is in accord with the experimental results of von Tabora (148).

Hirschfelder (80) investigated the action of the drug on dogs in which auricular fibrillation was produced by faradization and found that the irregularly beating ventricles were markedly slowed by digitalis, but the rapid arrhythmia promptly returned when the vagi were paralyzed by atropin. Further slowing was obtained by very large doses of digitalis after atropin had been given and complete heart block with slow ventricular rhythm could be induced. Cushny (31) performed similar experiments with cats and found that after the vagi had been cut, strophanthin failed to remove the irregularity and acceleration of the ventricles until a late phase of the action of the drug set in, with auriculo-ventricular dissociation. He contends, however, that these experiments are not comparable to auricular fibrillation in man in which malnutrition of the cardiac tissues presumably exists.

It has been suggested that digitalis is especially potent in blocking impulses sent down by the fibrillating auricles. In order to determine whether this is true Robinson (127) studied the effect of vagus stimulation in dogs, both with normally beating hearts and with auricular fibrillation induced by faradization of the auricles. The results were recorded by electrocardiograms. The experiments show that the type of auricular activity has no influence on the degree to which impulses are blocked by vagus stimulation. In the light of these experiments it would seem that the character of the auricular activity, whether coördinated or fibrillary, plays no part in the effectiveness of digitalis in depressing conduction by stimulation of the cardo-inhibitory centre.

An examination of the evidence bearing on the question of the manner by which digitalis reduces the ventricular rate in auricular fibrillation must lead to the conclusion that various phases of the subject remain unsettled, and little or nothing is known regarding certain of its aspects. It seems established that the ventricular slowing is brought about by the dual action of digitalis on the cardio-inhibitory centre and directly on the conduction pathway, but the

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relative importance of these two effects is not clearly understood. Furthermore, it is not yet determined to what extent cardiac malnutrition or other changes in the heart influence the action of the drug, nor what relation exists between the ventricular slowing in cases of auricular fibrillation produced by bodily rest and that caused by digitalis. A clearer understanding of these problems would doubtless place the use of digitalis in auricular fibrillation on a more intelligent basis, and would probably lead to its more effectual employment.

There is some evidence in favor of the belief that digitalis may be beneficial in cases of auricular fibrillation independent of the ventricular slowing it produces. Edens (37) for instance, has observed clinical improvement without any diminution of the ventricular rate. Increased efficiency of the ventricular contraction by the direct action of the drug on the heart muscles may play some part in its valuable effects in this condition.

Patients with auricular fibrillation are not all equally susceptible to the beneficial effects of digitalis. The cases may be roughly divided into two groups, those in which auricular fibrillation follows the so-called rheumatic infections and those in which arterial sclerosis, with presumably accompanying cardio-sclerosis is present, and frequently with a preceding syphilitic infection. The first group is composed, as a rule, of young or middle aged persons who show very rapid ventricular rates. Cases of this group are, as a rule, those that show the most striking benefit from digitalis. The cases of the second group may be much less benefited. They do not show such high ventricular rates, and, in some cases, it is not above the average normal level, although evidences of heart failure are well defined. Mackenzie (109) who first pointed out this distinction, attributed the difference to changes in the cardiac muscle, and holds that the reaction to digitalis is much more easily induced in cases with presumably slight myocardial damage than in cases with extensive degeneration. This distinction is undoubtedly correct, but it does not take into account the state of the conduction pathway, which is presumably more damaged in the second group of cases than in the first. Digitalis is often of little value in cases in which the ventricular rate is slow before digitalis is given. In these cases, the tissues involved in the

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conduction of the cardiac impulse are damaged and are therefore not capable of transmitting impulses at a rapid rate. This damage may be taken as an evidence of a widespread involvement of the myocardium which is unable to maintain an efficient circulation even when the ventricles are contracting slowly. Under these circumstances, further slowing may cause no improvement in the circulation, and sometimes may be distinctly harmful.

On the other hand, in many cases of auricular fibrillation, the myocardium is sufficiently preserved so that the ventricles can maintain the circulation efficiently when their rate is held within bounds by digitalis. Certain conclusions regarding prognosis are justified therefore from the response to the drug. Patients should be studied with this point in mind. Physicians should also learn to distinguish between cases in which excellent results are to be expected from those less liable to benefit, before drawing conclusions as to the efficiency of the preparation of the drug being used.

The ventricular rate, in many cases, can be regulated at will by the amount of digitalis administered. The optimum rate and the doses required to maintain it, must be determined by trial in each case. The dosage has to be varied frequently, and no rule applies to all cases. The proper amount of the drug to be given is to be determined by the effect of various doses on the symptoms of heart failure and by the ventricular rate.

It must be borne in mind that the radial pulse cannot be relied upon for determining ventricular rate, as when the ventricles are beating rapidly and irregularly, many contractions may fail to produce a palpable pulse at the wrist. For this reason the ventricular rate should always be determined by counting the number of heart beats per minute by means of the stethoscope. It is very useful in following the effect of digitalis in auricular fibrillation to determine the number of ventricular contractions that fail to produce a palpable pulsation at the wrist. The number of such beats per minute constitute the so-called pulse-deficit, a term invented by George Draper (personal communication). A pulse deficit of 20, 30 or more a minute is often found in untreated cases, and the disappearance or reduction of the pulse-deficit should be taken as an important guide for the proper dosage of digitalis.

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It is usually desirable to reduce the ventricular rate to between 70 and 80 beats per minute, although some cases seem to have a better state of cardiac efficiency when the rate is higher, and Pratt (122) has found that the circulation is sometimes best maintained at a rate much lower than that of the normal heart. In one of his patients under constant administration of digitalis, the heart rate was rarely above 50 per minute during a period of two years.

The constant employment of digitalis is usually necessary to keep the ventricular rate continuously slowed, and the benefits of constant use of digitalis have been pointed out by Schmoll (141), Borultau and Stadelmann (7), Fulton (56), Pardee (117) and others. Pardee has brought out the fact that the body must be kept nearly full of digitalis and not nearly empty, and in order to accomplish this, the drug must be given at a rate comparable to that of its elimination from or destruction in the body. Fulton (56) remarks that many cases need continuous administration of the drug and by the use of small doses the heart may be controlled so that the patient may be able to go on with his ordinary routine of life indefinitely.

It is certainly one of the most gratifying experiences in medical practice to see the great benefit digitalis frequently brings about and maintains in these patients for months and years by its constant administration in doses so regulated that toxic symptoms do not appear, while the heart is kept continually under its influence.

Excessive amounts of digitalis in auricular fibrillation may produce complete heart-block, causing the ventricles to assume a regular rhythm at an excessively slow rate. Taussig (149) has reported two such cases in which permanent complete block developed during digitalis administration. Slow regular ventricular action occurring in cases of auricular fibrillation during digitalis medication should always be taken as an indication of excessive action of the drug and should lead to its discontinuance. Complete heart-block may occur without other evidences of intoxication, as happened in a case reported by Robinson (128).

Another disturbance of the heart beat which is prone to follow the administration of the drug in cases of auricular fibrillation is the so-called bigeminal pulse or coupled rhythm. It may appear when relatively small amounts of the drug have been given, which do not

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ordinarily produce toxic symptoms. The absolutely irregular rhythm is replaced by pairs of beats followed by pauses of varying lengths. There is usually a fairly constant time relation between the coupled beats. Coupled rhythm may be detected by the study of the heart sounds and radial pulse as Christian (14) has stated, but electrocardiograms reveal their true nature. Coupled rhythm is produced by the occurrence of a premature contraction of ventricular origin following regularly each ventricular beat stimulated by the auricles. Its occurrence is to be taken as a sign for discontinuing digitalis.

Edens and Huber (38) have studied this phenomenon and consider that it probably only occurs in hypertrophied insufficient hearts. They regard its occurrence with relatively small amounts of digitalis as an unfavorable prognostic sign. They found that coupled rhythm was always dependent on ventricular premature contractions which resulted, they believed, from an increase in the irritability and stimulus formation in the ventricles produced by digitalis in damaged hearts where there was a high calcium content in the blood. The amount of the drug producing coupled rhythm was quite variable.

The beneficial action of the drug on the peripheral circulation in auricular fibrillation has been demonstrated by Stewart and Scott (145) who studied the blood flow in the hands by means of calorimeters. They found that in three of four cases, the blood flow was increased in the hands within twenty-four hours after the tincture of digitalis was given. This finding is merely a quantitative corroboration of the effects of the drug when determined by the clinical study of signs and symptoms of heart failure.

The striking action of the digitalis bodies in slowing the ventricular rate in auricular fibrillation has been put to useful purposes in studying certain aspects of the digitalis problem, as the ventricular slowing usually occurs as a sharply defined reaction on the part of the heart which may be readily distinguished as of digitalis origin, the onset and duration of which can be determined.

b. Auricular flutter is a disturbance of the heart beat caused by an excessively rapid auricular rate, usually about 300 contractions per minute, accompanied by varying degrees of heart-block. Recent studies of Lewis, Feil and Stroud (102) indicate that auricular flutter is in reality closely allied to fibrillation. They interpret the very

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rapid auricular activity as dependent upon a continuous circuit of the cardiac impulse through the auricles, along a constant path at a rate constant for each case. They account in this way for the practically absolute regularity of the auricular rhythm which they have demonstrated, and for other features of this cardiac disorder. The ventricles do not participate in the excessive auricular rate, but may respond to every second, third or fourth auricular contraction. Flutter generally persists for months or years, and does not tend to cease spontaneously. The recognition of auricular flutter can be readily accomplished by electrocardiograms and less easily in polygraphic tracings. Without the use of graphic methods, it cannot be distinguished with certainty.

Digitalis has proved of definite value in treating cases of auricular flutter. Lewis (96) first showed conclusively that flutter passed into fibrillation during the administration of the drug, although Mackenzie (108) and Turnbull (150) had previously recorded cases of the same nature. In a later paper, Lewis (97) recorded other instances of this action of digitalis, and has pointed out that when fibrillation surplants flutter it is usually temporary and the normal cardiac rhythm may be resumed permanently. These observations have been frequently confirmed, and Lewis states that the production of fibrillation by digitalis administration is an important therapeutic measure in cases of flutter. The action by which auricular flutter is transformed into fibrillation is uncertain. The drug renders the auricles more liable to fibrillation than before, and this may be accomplished either by direct action on the auricular tissues or by its action through the vagi. It seems possible that the conduction of impulses through the auricles is interfered with and areas of block are produced, a change which is, according to recent investigations, an important factor in the causation of auricular fibrillation. When first set up, fibrillation tends to disappear, and in the cases under discussion the normal rhythm is resumed before fibrillation becomes, so to speak, firmly established. Lewis has shown that auricular flutter may be abolished by the administration of digitalis after it has persisted for months.

Digitalis may serve another useful purpose in auricular flutter as Lewis has also pointed out. With the auricular rate as high as 300 per

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minute the ventricles may respond to every second contraction, and so attain a rate of 150 beats per minute. Digitalis by its action on the conduction pathway between auricles and ventricles may increase the degree of heart-block which is already present, presumably because of the excessive auricular rate. After the depression of conduction the ventricles may respond to only every third or fourth auricular contraction and so be decidedly reduced in rate, much to the improvement of the cardiac efficiency. Thorough digitalization of patients with auricular flutter is therefore a valuable procedure whenever this disturbance of the heart beat is encountered.

c. Cardiac contractions of abnormal origin. Impulses leading to cardiac contractions may arise in some point in the auricles or ventricles quite outside the region of the heart in which the normal rhythmical stimuli are generated. Such impulses may arise occasionally or frequently at fairly regular intervals causing the single premature ectopic beat, or extrasystole, or they may arise rhythmically and so rapidly that they dominate the cardiac rhythm causing a high grade of tachycardia. These various conditions dependent upon cardiac contractions of abnormal origin will be discussed separately in their relation to the action of digitalis.

Premature contractions or extrasystoles occur in association with various cardiac disorders, as well as in hearts that show no other abnormalities. They have no material influence on the circulation when occurring only occasionally, but when frequent, as often for instance, as every second or third regular heart beat, they tend to lower the efficiency of the heart, often produce annoying subjective symptoms and are therefore undesirable. There are two questions that arise concerning the relation of digitalis to premature contractions. Has the drug any effect in preventing their occurrence and is their spontaneous occurrence a contraindication to the therapeutic use of the drug?

It has long been known that large doses cause premature contractions which are recognized as one of the most constant manifestations of the influence of the drug on the heart, and as such have been discussed previously. Although Wenckebach (155) was aware of this effect of large doses, he reported several cases, and published curves of two of them in which small doses of digitalis caused the disappearance

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of premature contractions after they had been present over long periods of time. He considered this effect as due to the direct action of the drug on the heart muscle. Mackenzie (109) has given digitalis to patients in whom spontaneous premature contractions of ventricular origin were occurring and was unable to observe any effect on them.

Edens (37) has perhaps studied the subject more closely than any one else. He reports the results of the use of digitalis in a variety of cases with premature contractions, and he has attempted to differentiate these cases on the basis of the possible causation of the premature beats. He concludes that premature contractions dependent upon recent rheumatic lesions of the heart are not influenced while those that appear to be associated with insufficiency of the coronary circulation are probably cleared up by digitalis. He found that the type of premature contractions that occur in persons who use tobacco excessively, the so-called nicotine extrasystoles, are not affected by the drug, and those occurring in nervous persons sometimes disappeared and sometimes were unaffected by digitalis. Edens considered that the variable effects are dependent upon the fact that there are different forms of premature contractions and that sharp differentiation on the ground of further experience is urgently needed. He considers that premature contractions should be taken as contraindications for the intravenous use of digitalis.

So little is known regarding the underlying causes of ectopic premature contractions that a satisfactory hypothesis regarding the means by which digitalis may effect them and the manner in which they may respond to the drug cannot be put forward. It is possible that the heart muscle may be rendered less irritable by the stimulation of the cardio-inhibitory centre, as Wenckebach (155) has suggested. The production of premature contractions by the direct action of the drug probably occurs in hearts not already disposed to them only after very large doses, approximately 50 per cent of the minimum lethal dose. It is possible therefore that this action does not come into play even in hearts showing spontaneous premature contractions, while other effects of the drug tend to cause their disappearance. Their presence should not be taken as a contraindication for the therapeutic dose of digitalis, although it should lead to caution, and

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should indicate a reduction of dosage. The favorable influence of digitalis in bringing about the disappearance of premature beats is not to be viewed with any great expectations of success, although in small doses it may have this effect in some cases. Christian (19) has stated that

> this question of the exact relation of digitalis to extrasystoles is one still under discussion. In most cases, extrasystoles are more an incident in, rather than a cause of cardiac decompensation and their presence can be neglected in considering the probable efficiency of digitalis therapy.

d. Paroxysmal tachycardia has been shown by electrocardiographic studies to be a disturbance of the heart beat dependent upon the mechanism closely allied to that responsible for the occurrence of single premature contractions. It is characterized by the sudden onset of a very rapid cardiac rate, usually between 150 and 250 beats per minute, which terminates as suddenly as it begins, the rate usually returning to normal after a period of some hours or days. Very short paroxysms are also seen. These periods of tachycardia are apt to recur, once they have been established. The tachycardia is brought about by the production of cardiac impulses in some point removed from the region of normal impulse formation. The ectopic focus generates impulses at an abnormally rapid rate, and assumes the rôle of cardiac pace-maker. The ectopic focus is usually in one of the auricles but ventricular foci have also been found to produce such paroxysms.

Digitalis has proved to be without influence on the high rate of the heart brought about by this disturbance of its mechanism. Edens (37) has reported a case in which the paroxysm stopped during digitalis administration, but the relation of cause and effect cannot be established. During the attack the degree of heart failure varies greatly from patient to patient; but, in most instances, when the attacks are not prolonged, the evidence of cardiac insufficiency is not marked. Individuals who have these paroxysms of tachycardia not infrequently show no definite evidence of heart disease between attacks, and have, presumably, hearts that can adjust themselves to the abnormal rate. In prolonged attacks, however, the heart may show signs of muscular fatigue, which may be considered as an indi-

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cation for the use of digitalis. Robinson and Hermann (133) have recently reported a case of prolonged tachycardia of ventricular origin in which digitalis was given without any beneficial effects.

e. Heart-block. The depression of conduction is one of the most definite effects which digitalis produces, as has already been brought out. Therefore in partial heart-block, when further interference with the passage of the cardiac impulses from auricles to ventricles is decidedly undesirable, digitalis is contraindicated.

Cases are occasionally seen in which the conduction time is lengthened on account of faulty nutrition of the functional tissues between the auricles and ventricles. This depression in conduction is comparable to that which occurs during asphyxia, and may disappear with an improvement in the state of the circulation. In these cases digitalis has been observed to bring about an improvement in the auriculo-ventricular conduction, and to shorten the conduction time to within normal limits. Careful study by those experienced in abnormal cardiac physiology is necessary to differentiate these cases from those showing depression of conduction produced by structural changes in the conducting system.

In complete heart-block, when the ventricular contractions are being stimulated by the inherent rhythmicity of the ventricles, the action of the drug on conduction may be disregarded. Under these conditions an improvement of the efficiency of the ventricles and especially the quickening of their slow rate is the result to be desired, and there is evidence to show that this may sometimes be attained by digitalis.

Jagic (82) noted improvement of a patient with complete heart block when small doses of digitalis (0.05 gram per day) were given. Martinet (110) has also advocated the use of digitalis in complete heart-block, and has warned against its use when the block is partial. He believes that digitalis acts both on the vagi and directly on the heart muscle, and he points out that the latter action may be effectual in complete heart-block while the independently beating ventricles are not under the control of the vagi, and so the former action can be disregarded. Bachmann (3) has studied a case in which strophanthus was given with beneficial results and with an increase in the ventricular rate while the auricles were slowed. Bachmann (4)

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reported a second case with similar results, in which the ventricular rate increased from 23 to 31 beats per minute during the administration of the drug. He is of the opinion that strophanthus is of more benefit in complete heart-block than digitalis.

Hewlett and Barringer (79) report a case in which digitalis produced auriculo-ventricular dissociation and in which the ventricular rate exceeded that of the auricles. They suggest on the basis of this observation that the drug may be of value in complete heart-block. They failed, however, in the one case that afforded them an opportunity of testing their hypothesis to get any increase in the ventricular rate following the administration of digitalis.

Cushny (29) has suggested that helleborein might be especially useful in heart-block, as he says it has an effect on the heart muscle similar to that of digitalis, but is without effect on the cardio-inhibitory mechanism. Recent investigation of cases of complete heart-block have shown that the rate of the independently beating ventricles is, in most instances, free from the control of the vagi, and therefore the inhibitory action of digitalis should not be considered of moment in these cases. The direct action of the drug on the heart muscle may be advantageous in increasing the output of the heart even without a change in rate. Complete heart-block is not a contra-indication for digitalis according to Mackenzie (108) but the drug should be withheld in cases of temporary heart-block where a return of the normal heart beat is anticipated.

3. Heart failure with normal cardiac mechanism

a. Myocardial insufficiency is the name now frequently applied to that form of heart disease in which the power of the heart muscle is apparently impaired, and in which no other cause can be discovered to account for the failure of the heart to maintain the circulation adequately. The term myocarditis has been used to express the same condition, but myocardial insufficiency is to be preferred, as it expresses functional rather than structural damage of the heart. In many instances, no satisfactory explanation can be found by the present day methods of examination of tissues for obvious myocardial inefficiency on the basis of structural changes in the heart muscle.

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In the case under consideration, ample evidence of heart failure is present, while there is no conspicuous disturbance of the cardiac mechanism, no demonstrable structural damage to the valves, no alterations in the vascular system sufficient alone to account for the symptoms. The patients, who are usually past middle life, are short of breath, unable to lie flat in bed and often have anginal pain, especially on exertion. They frequently have edema and cyanosis, evidence of congestion of the lungs and liver, with hydrothorax and, at times, ascites.

The heart is enlarged and the character of the heart sounds may be altered. There is often a systolic murmur at the apex. The urine usually contains albumen and casts, and there may be other evidence of renal insufficiency. The blood pressure is frequently elevated and the heart rate is often increased.

The clinical picture may vary considerably and only the most obvious symptoms have been enumerated in order to define this frequently encountered condition. The value of digitalis in the type of myocardial insufficiency that has been described is not nearly so well established as it is in cases of heart failure with auricular fibrillation. This is to be expected, as heart failure in these cases is dependent upon some fundamental change in the cardiac muscle which no known means can remove; while in auricular fibrillation a definite factor of heart failure can be altered advantageously. The difference in the effects of digitalis in these two types of heart disease is noted consistently in the literature on digitalis since it was first brought out by Mackenzie (108) in 1905, and since these types have received definite clinical differentiation.

The prime object in the use of digitalis in myocardial insufficiency is to improve the ability of the heart in propelling the blood and in restoring the balance between the arterial and the venous side of the circulation. It has already been shown how difficult it is to obtain any definite direct evidence of changes in the output of the heart. Various elaborate methods have been devised for its indirect determination, but these have not been extensively used in the study of the problem now under consideration. It is necessary therefore to rely on the improvement of symptoms by digitalis, and this evidence is often difficult to evaluate.

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It has been repeatedly shown by Cushny (29), Mackenzie (109), Edens (37), Pongs (120), Cohn (20), Pratt (122), Christian (16) and others that the cardiac rates of these cases is usually not slowed by digitalis, and the action of the drug on the cardio-inhibitory mechanism apparently plays as a rule no part in the favorable results which the drug may accomplish in cases with regularly beating hearts. Cohn (20) has emphasized the importance of differentiating cases with edema from those without it, and there is general agreement that in cases of myocardial insufficiency with edema, diuresis follows the administration of digitalis, the edema is diminished or disappears and there is a general improvement in symptoms. At the same time, the idea prevails, as recently stated by Eggleston (47) that the diuretic action of the drug is essentially secondary to its capacity to relieve heart failure and to restore the circulation. Diuresis must be looked upon, if this idea is correct, as evidence of a beneficial influence of the drug on the heart muscle, although this conclusion is not as yet warranted as final. This question has already been discussed.

The various statements of those who have studied properly the effect of digitalis in myocardial insufficiency indicate that benefit is often derived from its use, but the manner of its action is still obscure. Cushny (29) noted improvement in such symptoms as dyspnea, cyanosis and edema without any change in the cardiac rate, and attributed the improvement to the direct action of the drug on the heart muscle. Edens (37) also observed clinical improvement without slowing of the heart rate, and he believes the contractility of the heart is effected favorably by digitalis, but considers that myocardial damage limits its influence in this regard. Cushny's (31) later work emphasizes the relation of malnutrition of the heart to the action of the drug, and he believes the drug is more likely to act directly on the heart when malnutrition is present. Mackenzie (109) has always been skeptical regarding the idea that heart failure may be relieved by the effect of the drug on the heart muscle. Christian (15) in discussing what he terms chronic myocarditis says that it constitutes a group of cases in which digitalis is very effective, whether auricular fibrillation is present or not, but with recurrences of heart failure the drug becomes less and less able to bring relief. Windle (162) has also observed definite improvement in the cases under

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discussion, but says that the improvement in advanced cardiac failure is often only temporary, and the drug becomes less and less effective as the cardiac inefficiency advances. Christian (16) has recently reported a series of cases of myocardial insufficiency with regularly beating hearts and with edema in which digitalis produced satisfactory effects.

Pratt (122) has employed strophanthin intravenously in these cases, and says that as improvement has occurred in forms of heart failure that are rarely, if ever, relieved by digitalis, it is suggested at least that strophanthin given intravenously exerts an effect on the contractility or tonicity of the heart muscle that is not obtained from digitalis in therapeutic doses. West and Pratt (156) have recently remarked that there is little doubt in the minds of most clinicians that much good can be expected from proper dosage in patients showing regular rhythm, when their symptoms are evidence of heart failure. They gave full doses of dried aqueous extract of digitalis to a number of such patients and in many obtained effects that were quite as gratifying as in those showing auricular fibrillation.

The heart is often unusually susceptible to digitalis in the class of cases under consideration, and toxic effects may be produced by relatively small doses, so that careful study of these cases is especially necessary when digitalis is administered. It is evident that digitalis is of definite value in cases of heart failure dependent upon myocardial insufficiency, especially when edema is present. The manner in which the drug acts is still a matter of uncertainty. The fact that abnormalities exist in the heart which have not as yet been closely duplicated in animals renders comparison with experimental results unwarranted. The influence of digitalis in cases of myocardial insufficiency needs further study.

b. Pulsus alternans, a phenomenon dependent upon myocardial weakness, consists of an alternation in the regularly beating heart of relatively strong and weak cardiac contractions which gives an alternating character to the radial pulse. This abnormality of the cardiac contractions is a grave sign of myocardial insufficiency. It has been observed following the administration of digitalis, apparently as an effect of the drug; and as such it has already been considered as a toxic effect. Questions have been raised as to whether the

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presence of pulsus alternans is a contraindication for the use of digitalis and what effect the drug has upon it when already present. Windle (162) has made an extensive study of these questions. He considers pulsus alternans as being invariably the expression of an overtaxed heart, and says that it is the only form of pulse rhythm giving definite information regarding the functional efficiency of the heart. Windle was among the first to demonstrate the fact that the presence of pulsus alternans is to be considered a sign of impending death, even when circulatory failure is not extreme. He has studied the effect of digitalis in over 100 cases of heart failure showing alternation, and although the condition does rarely follow the administration of the drug, he never found that digitalis increased the alternation of the pulse or produced harmful effects when it was present. On the contrary the alternation and irregularity in rhythm of the pulse frequently became lessened, and not seldom was abolished. The presence of high blood pressure does not contraindicate the use of the drug in these cases. Windle points out the relation of rate to alternation, and shows that as the diastolic periods of cardiac rest lengthen, the tendency to alternation of contractions diminishes. On the other hand, the slower the rate at which alternation is observed, the more serious is the prognostic significance, as the more extensive exhaustion of the heart muscle is indicated. Pulsus alternans may disappear permanently under digitalis in cases of myocardial damage following rheumatism, but Windle believes it practically never permanently disappears in aged patients. Christian (14) who publishes some excellent records of pulsus alternans, has obtained good results in patients showing this phenomenon. He reports a case in which digitalis produced striking slowing with definite clinical improvement, but without disappearance of alternation. Christian remarks that it is to be remembered

> that a pulsus alternans is a sign of a very much impaired myocardium, and when the myocardium is greatly impaired the likelihood of functional improvement from digitalis is much decreased. To push digitalis in such a case may do much damage. Here it is particularly difficult to judge how far to carry digitalis therapy if no evident effect is produced. It would seem that in many of these cases the margin between no therapeutic effect and a serious toxic effect is a very narrow one.

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Windle, in the light of an extensive experience, advises, on the other hand, to continue the drug until vomiting or coupled rhythm occurs.

4. Valvular heart disease

Valvular heart disease as such is not an indication for the employment of digitalis. Much misconception has been prevalent in medical practice regarding this fact. On the other hand, many cases with structural changes in the valves are much benefited by digitalis when heart failure follows or accompanies valvular defects. No one can conceive that the condition of the valves can be altered by the drug, and the presence of a valvular murmur, even when it is dependent upon a structural change in a valve, is never to be taken as a reason for giving digitalis. Experimental destruction of one or more of the heart valves in animals is not followed, as a rule, by marked disturbances of the circulation. However, under these conditions, the heart is otherwise undamaged, and is able to compensate for the faulty valves.

In patients with valvular disease the myocardium and the coronary arteries are likely to participate in the damage that has affected the valves, and share in the causation of heart failure. Various disturbances of the heart may therefore occur when valvular disease is present, and these disturbances rather than those of the valves should serve as an indication for the use of the drug. This is the attitude expressed by all students of the drug who have considered this matter, but it has not been discussed in the recent literature, because no doubt it has appeared self-evident.

One possible benefit of digitalis in valvular heart disease has, however, been recently suggested by Cohn and Fraser (22). They point out that a delay in the conduction of the cardiac impulse from auricles to ventricles may be of advantage to the heart when mitral stenosis is present, as such an effect would increase the time available for the left auricle to empty itself before the onset of ventricular contraction. They suggest that the action of digitalis in bringing about this delay of conduction may be a factor in its beneficial effect in cases of mitral stenosis, and that by the proper regulation of dosage, the conduction time may be constantly lengthened. No observations bearing directly on this suggestion have as yet appeared.

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One form of valvular disease, aortic regurgitation, has gained the reputation of being a contraindication for digitalis. This tradition no doubt goes back to the original description of the lesion by Corrigan (27) in 1832, for there he says that digitalis lengthens diastole and so allows more blood to regurgitate through the incompetent valve. All of his patients with this lesion who received the drug seemed to have become worse from its action. Corrigan does not state, however, that the heart rate can be slowed by digitalis. Christian (16) has commented on this subject and says:

> There still lingers the tradition that aortic insufficiency contraindicates digitalis, because digitalis would prolong diastole and the large regurgitant flow of the blood under these conditions would stop the heart in diastolic paralysis; a good enough theory; only it seems to have no basis in fact.

Pratt (121) also states that this lesion is not a contraindication for the use of digitalis, and this has been the general experience of all who have paid particular attention to this subject.

It may be said therefore that in determining the indications for the use of digitalis, valvular lesions as such should be ignored, and other evidences of cardiac disorder should always serve as the guides for the use of digitalis in valvular heart disease. However, the suggestion of Cohn and Fraser (22) concerning the possible value of the drug in mitral stenosis is worthy of consideration and careful study.

5. Disturbances of the nervous mechanism

Certain disorders of the heart are encountered in which without any disturbance of the cardiac mechanism, the heart assumes an abnormally rapid rate. The underlying cause of these disorders is not well understood, but the more prominent symptoms seem to be dependent upon a functional derangement of the nervous mechanism controlling the heart, and are perhaps caused by an overbalancing of the inhibitory nerves, the vagi, by the accelerators. Two examples of such disorders seem worthy of consideration: the so called effort syndrome or neuro-circulatory asthenia, and hyper-throidism, since digitalis has been employed in the hope of lessening the tachycardia in each instance.

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a. The effort syndrome is a condition which has come into prominence during the years of the recent war. It seems to be particularly prone to occur in young men of military age under emotional stress and strain incident to war, and affects probably those whose nervous make-up renders them predisposed. The chief symptoms consist of palpitation of the heart with tachycardia, breathlessness and cardiac pain on exertion, and manifestations of a disturbed nervous system, such as headache, giddiness and disturbed sleep. The symptom complex serves as a good example of what is generally called a cardiac neurosis, and because the more prominent symptoms are referable to the heart, digitalis has been used, especially with the idea of overcoming the tachycardia. Parkinson (119) has reported a study of the effects of digitalis on these cases carried on at the English Heart Hospital at Colchester, which was under the direction of Sir Thomas Lewis. Parkinson's results and conclusions serve as an example of the general experience with the use of digitalis in this condition. He administered full doses of the drug to a series of 20 patients. The heart rate was reduced but little, and the increase of rate which occurred with exercise or with standing was not controlled, to any appreciable extent, by digitalis. There was no effect on either the systolic or diastolic blood pressure. Parkinson states that digitalis scarcely influences this group of patients, even when the pulse is rapid, and he concludes that it is not indicated in the condition known as effort syndrome or neuro-circulatory asthenia.

b. Hyperthyroidism or exophthalmic goitre serves as another example of tachycardia which is primarily independent of any anatomical lesion of the heart or of any alteration in the mechanism of the heart beat. Several possible causes present themselves. The toxic substance generated by the thyroid gland may act directly on the heart or its nervous mechanism, producing the characteristic acceleration of rate; or there may be some fundamental change in the nervous system which manifests itself in part by causing tachycardia; or the increased cardiac rate may be secondary to the generalized increase in metabolic processes of the body. Without a better understanding of this subject, no rational therapy directed at the heart alone can be devised. Digitalis has been used with the hope of slowing the heart rate; but, as Cohn (20), Fulton (56) and others have pointed out, always without success.

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It may be said that not only in the two examples of cardiac neuroses that have been considered, but in all types of disturbances of the nervous mechanism, digitalis fails to produce any beneficial effects. The tachycardia, usually the most prominent symptom, is not influenced by the drug. Whenever the diagnosis can be established with certainty, if should be considered unwise to use digitalis in the cardiac neuroses with any expectation of obtaining beneficial results.

X. DIGITALIS IN INFECTIOUS DISEASES

1. Fever in relation to the action of digitalis

During the course of severe infections, the possibility of heart failure is naturally constantly before the physician. Digitalis has been used both as a preventive measure with the idea of "supporting" the heart through a period of unusual strain and also as a curative measure when signs of heart failure have appeared as a complication of an infectious disease. In this connection, the relation of fever to the action of the drug has been a matter of discussion. Cohn and Jamieson (24) have reviewed this subject and state that definite differences of opinion exist among American, English and German clinicians. Some consider the drug is without power in the presence of fever; while it has been used extensively by others, especially in pneumonia. Mackenzie (109) states that digitalis has little effect upon the heart rate when it is elevated by agents which increase its excitability, and cites the effect of fever as an example. Cushny (30) also says that digitalis is especially apt to be inefficient when fever is present.

Cloetta (19), however, has recently recommended the use of digitalis in acute infections, combined with camphor and believes that it is important to begin the administration early in the course of acute infections. His recommendations are apparently based on somewhat empirical reasons however.

The relation of the body temperature to the action of digitalis has been subjected to animal experimentation. According to Jamieson (83), Gunn studied the effect of strophanthin on the perfused heart at temperatures ranging from 28° to 41°C. and found that the drug acted more quickly at higher temperatures. Recently Hirschfelder,

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Bicek, Kucera and Hanson (81) have studied the effect of high temperature on the action and toxicity of digitalis. They injected the tincture intravenously into cats, the body temperatures of which were elevated by immersion in water, heated to 43° to 46°C. They found that digitalis produced effects in these animals similar to those observed in normal animals, but there was a decided influence on the minimal lethal dose per kilo of body weight which is shown in the following table.

TEMPERATURE	AVERAGE LETHAL DOSE
°C.	*cc. per kilogram*
37–39	0.94
41	0.78
42	0.59
43	0.375

On the basis of these results Hirschfelder and his collaborators warn against giving large doses of the drug to patients with high temperatures.

2. Pneumonia

Pneumonia is the infectious disease in which digitalis has been most extensively used, and in which its action has been especially studied. These studies furnish valuable information regarding the action of digitalis in the presence of fever.

Fulton (56) in 1914 expressed the general opinion prevalent at that time regarding the employment of the drug in pneumonia.

> Where there is cyanosis with low blood pressure and a rapid, feeble pulse, the question always arises whether digitalis should be administered. The evidence in regard to its value in such cases is not satisfactory. It is not likely to do harm unless there is some involvement which might encourage the formation of heart-block, in which instance it should not be used.

Since this time, Cohn and Jamieson (24) have carried out a systematic study of the action of the drug in pneumonia, and have obtained results that give definite answers to the questions involved. They studied a series of 105 cases of pneumonia, 49 of which received digitalis, while 56 cases served as controls and were studied with

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equal care. Electrocardiograms were obtained at frequent intervals, and particular attention was paid to the length of the conduction time, variations in the T wave of the electrocardiogram and the ventricular rate in cases of auricular fibrillation.

Digitalis was given by mouth in the form of digipuratum. They state:

> In general the criteria we employed permitted us to judge satisfactorily whether digiatlis was acting. We found that the signs appeared after the same amount had been given and following the same length of time in which these signs appeared in non-febrile cases originally studied. When no digitalis was given the signs did not appear.

Cohn and Jamieson conclude that digitalis acts during the febrile period, and produces a beneficial, possibly a life-saving effect when auricular fibrillation or flutter occurs during the course of pneumonia. Whatever beneficial action digitalis has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart in pneumonia.

Cohn (21) observed auricular fibrillation or flutter in 12 out of 123 cases of pneumonia; or in practically 10 per cent. He considers the frequency of these cardiac derangements in pneumonia sufficient ground for keeping patients under the influence of digitalis during the course of this disease. The drug was consequently routinely administered to pneumonia patients according to the following plan, the dose being indicated in grams of the leaf.

	DAY OF DISEASE								
	1	2	3	4	5	6	7	8	9
If seen early	0.5	0.5			0.5	0.5			
If seen late				1.0		0.5	0.5		

Stone, Phillips and Bliss (146) studied the effect of digitalis in a large series of cases of pneumonia in an army hospital during the recent war. They attempted to digitalize thoroughly the cases during the first forty-eight hours in the hospital by administering 0.17 cc. of a standardized tincture per pound of body weight in several large doses. The total amounts ranged from 20 to 30 cc.

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With these doses vomiting occurred in only 4 to 5 cases; partial heart-block appeared in one, and there was a considerable rise of blood pressure in another. There were 871 cases in their series and the administration of the drug was begun at a certain date after about half the number of cases had been seen. The conditions under which these patients were observed did not allow detailed study but there was a striking difference in the death rate after the use of digitalis was begun. This is shown in the following table:

	BEFORE THE USE OF DIGITALIS	AFTER THE USE OF DIGITALIS
	per cent	*per cent*
Deaths not associated with sepsis	25.8	11.8
Deaths from uncomplicated pneumonia	17.1	11.2
Deaths from pneumonia complicating measles	46.3	14.8

Stone and his co-workers believe the tincture of digitalis was responsible for the decrease in the percentage of deaths in the cases not associated with empyema or other "septic" conditions, being definitely valuable in the type of cases whose deaths are associated with cardiac failure.

Caution must be exercised in drawing sweeping conclusions from this study, as under the circumstances, it cannot take into account certain possibilities such as variations in the virulence of the infecting organisms or other conditions altering the severity of the infections.

Jamieson (83) carried out an investigation on the action of the lethal dose of strophanthin in normal animals and in animals with experimental pneumonia. Cats and dogs were used and strophanthin was given by intravenous injections. Pneumonia was produced by intratracheal insufflation. Jamieson studied the effect of strophanthin in 21 cats that were not given pneumonia and 12 animals were studied that had pneumonia but were not given strophanthin. The action of the drug was studied in a large series of infected animals. The results of these experiments led to the following conclusions:

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from experimental pneumonia.

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2. The minimal lethal dose is the same in normal dogs and in dogs suffering from experimental pneumonia.

3. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.

4. Electrocardiographic changes occurring in the heart's action when strophanthin is injected are found to be similar in normal and in infected animals.

5. The identity of strophanthin action in infected and in normal animals renders it probable that a like similarity may be anticipated in man, under normal conditions and in pneumonia.

This work corroborates the idea expressed by Cohn and Jamieson that the action of digitalis is the same in pneumonia as it is under non-febrile conditions. Probably the unfavorable influence of fever on the action of digitalis arose from the observations that the drug failed to slow the heart in febrile conditions, but it is now known that the drug usually fails to slow the normally beating heart when fever is not present except under special and rare conditions. Further work is necessary to substantiate the idea that digitalis "supports" the heart during pneumonia, although the work of Stone, Phillips and Bliss is suggestive and Cohn considers it desirable to give the drug to patients with the disease in anticipation of auricular fibrillation. The question may be raised, however, as to whether such use of digitalis may not tend to bring on auricular fibrillation in these cases.

3. Diphtheria

Diphtheria is another infection which deserves special consideration because of the frequency of cardiac damage as one of its most severe complications. The view has been held for a long time that the drug does not benefit the cardiac disorders following diphtheria and is possibly harmful in this condition. Only recently, however, has this matter been subjected to careful study by modern methods. McCulloch (111) after an extensive study of the heart in diphtheria by means of the electrocardiograph, and after many careful observations on the effect of digitalis in children, has drawn attention to the close similarity between the cardiac disturbances produced by diphtheria and the toxic effects of digitalis on the heart. In diph-

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theria presumably through the action of the toxin on the heart, conduction is often damaged, premature contractions frequently occur, or there may be striking changes in rate, either a high grade of tachycardia or marked slowing. McCulloch attributes the slowing of the heart in diphtheria to vagus stimulation, and he has studied the effect which atropin has upon it. This interpretation is perhaps open to question. There is, however, such a close resemblance between the effects on the heart of diphtheria toxin and of digitalis that it seems to be adding insult to injury to administer the drug to patients with the cardiac complications of diphtheria. McCulloch's paper is a valuable contribution to the knowledge of indications for the use of digitalis.

XI. DOSAGE OF DIGITALIS

1. Oral administration

a. The amount of the drug. Withering laid down a sound principle for determining the proper dosage of digitalis when he wrote, "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." He recognized the necessity of regulating the dose of the drug by its action, rather than by accepting a standard dose as applicable for various samples of the drug and for various types of disease in which it might be employed. In spite of his directions, standards of dosage of wide variations have been advocated.

Eggleston (42) states that the doses of the tincture of digitalis recommended by recognized authorities range from 2 minims (less than $\frac{1}{4}$ gram of the leaf) three times a day to 30 minims (3 grains of the leaf) three times a day; the larger dose being fifteen times as great as the smaller. Hatcher and Bailey (72) have discussed the use of the tincture of strophanthus and strophanthin, and have drawn attention to the great diversity of opinion regarding the dosage of these drugs, and to the apparent confusion relative to the activity of various preparations. It seems probable that variability of absorption is largely responsible for the lack of uniformity of dosage, as will be brought out later. It is apparent that many misconceptions have existed regarding the dosage of digitalis and its allies.

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There has been recently a tendency to attribute poor results of digitalis to its use in inadequate doses.

During the past few years considerable attention has been focused on the matter of dosage, and much progress has been made towards establishing sound principles, based on accurate determinations in the laboratory and in the clinic. Eggleston and Hatcher deserve a large share of the credit for this progress, and their contributions to various phases of the subject have proved of much value.

The fundamental problem involved in the dosage of digitalis is the determination of the average amount of standard preparations required to produce maximum therapeutic results in the types of patients to whom the drug is usually given and which does not produce severe toxic symptoms. The method that has recently come into use is essentially the same in principle as that advocated by Withering, and consists in the administration of the drug to series of patients until well defined evidence of digitalis action appears. Modern methods, however, allow the detection of specific effects of the drug with greater precision and at an earlier stage than was possible in Withering's day.

After the determination of the average amount of the drug necessary to produce the desired effects in a series of patients, attempts have been made to convert this finding into a rule designed to allow others to employ the drug in the amount most likely to benefit similar patients, and to allow its use under conditions which do not permit the determination of the early evidences of its toxic action.

Following such carefully conducted studies as those of Mackenzie (109), recommendations as to dosage were made which reflected the results obtained in each series of patients. All of the students who employed accurate methods for the detection of digitalis action advocated larger doses than had been previously customary, but the earlier students of the present period of accurate objective clinical observation pointed out the fact that the dose must not only be fairly large but also that the drug must be continuously administered until definite effects were produced, when it should be either discontinued or much reduced in amount.

The study of Eggleston (42) marks the beginning of much progress in digitalis dosage. His paper published in 1915 brought out a

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number of points of permanent value, and is an excellent example of clinical observation based on a sound training in the pharmacological laboratory. Eggleston undertook to determine whether or not it was possible to establish the dose of digitalis for man on the basis of the activity of the drug as determined by a biological assay. He studied, at the same time, several other problems directly concerned in the question of the dosage of digitalis and its allies and pure principles. These problems were:

1. The rate, degree and uniformity of the absorption of the crude drug and its active principles.
2. The influence of sex, age and weight on the dose.
3. The influence of the preparation-infusion, tincture, etc., on the dose.
4. The influence of the cardiac condition.
5. The influence of the size of the daily dose on the total dose required.

Eggleston used tinctures and infusions of digitalis, made from leaves of different sources and varying in activity, and crystalline digitoxin dissolved in 70 per cent alcohol or made into tablet triturates. The activity of each preparation was determined in terms of cat units by the method of Hatcher and Brody (74). These drugs were administered by mouth to a series of patients, some of whom had auricular fibrillation. Care was taken that none of the patients had received any one of the digitalis group of drugs within a period of not less than three weeks prior to the beginning of the observation. The patients were kept under observation in bed for from three to seven days before digitalis or digitoxin was given, whenever their condition justified such a period without medication. Body weight, intake and output of fluids, blood pressure, polygraphic—and in some instances—electrocardiographic records were obtained as indicated, as well as frequent physical examinations. Personal bias was, as far as possible, eliminated in judging changes in the condition of the patients.

The study was carried out on 47 patients, 6 of whom had two courses of treatment, making 53 in all. Fifteen studies were made on cases with auricular fibrillation and 38 on non-fibrillation cases.

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The action of digitalis was determined by subjective and objective improvement in the symptoms and signs of heart failure and in the appearance of minor toxic effects. The phenomena included in this latter category were marked sinus arrhythmia, partial heart-block, premature contractions, nausea and vomiting.

The details of the method used by Eggleston are given because his work is a good example of the methods of clinical studies which have yielded valuable results, and indicate the various procedures necessary to prevent faulty observation and false conclusions when studying the effect of these drugs on patients.

The most important feature of Eggleston's study is that it enabled him to determine the amounts of the drugs in terms of cat units per pound of body weight required to produce therapeutic and toxic effects. In other words, he introduced two quantitative factors into the consideration of dosage that had previously received only indefinite consideration, and had not been brought into accurate relation with each other. Eggleston brought to the problem of dosage drugs of known activity and measured their effects in terms of the total amount used in relation to the weight of the individuals receiving them.

No definite difference was found between the amounts of the drugs necessary to produce comparable therapeutic or minor toxic effects in cases with auricular fibrillation and in non-fibrillation cases.

Eggleston draws the following conclusions and deductions from his studies:

1. The cat method of standardization of digitalis yields results on which the dose for man can be based.

2. The average therapeutic dose of digitalis given orally to man in the form of tincture is 0.146 cc. of an average high grade tincture per pound of body weight as established by thirty-three observations.

3. Fifteen observations have established 0.066 cat unit, or 0.023 mgm., per pound as the average therapeutic dose of crystalline digitoxin.

4. Approximately half of a total of 48 courses of administration of either digitalis or digitoxin, full therapeutic effects were secured with doses falling within 15 per cent above or below the average dose.

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5. Doses considerably larger than the average were taken in 17 instances without the production of more than mild toxic symptoms.

6. The activity of the preparation of digitalis has no material influence on the dose required in terms of cat units.

7. Age, sex and cardiac condition do not seem to influence the size of the dose required.

8. Both digitalis and digitoxin are probably rapidly and fairly uniformly absorbed from the alimentary canal of man, but digitalis is less completely absorbed than is digitoxin.

9. Strophanthus, the strophanthins, ouabain, true digitalin, and some other digitalis substances are poorly or irregularly absorbed when given by mouth to man or to the higher animals and are unsuited for therapeutic use in this way.

Eggleston has pointed out the practical application of his results. In dealing with the tincture of digitalis, the dose may be taken for convenience as 0.15 cat unit per pound of body weight when the tincture possesses a strength of 1 cc. to the cat unit. This has been found to be the average strength of high grade tinctures and represents 100 mgm. of the crude drug. This strength may be accepted as a basis for the calculation of the total amount probably necessary to produce the maximum therapeutic results. A patient weighing 150 pounds would therefore require 22.5 cc. of such a tincture. Eggleston states:

> On the basis of the patient's actual or estimated weight, the total amount which would probably be required should be calculated and this quantity could then be divided into single or daily doses according to the rapidity with which it was desired to induce the full therapeutic effects. If, after the total calculated amount had been taken, the patient failed to show the full therapeutic effect or some minor toxic action indicated that enough had been given, the administration should be continued in small repeated doses until one or the other of these evidences called for its withdrawal.
>
> In this way it is possible to give a third to half of the total calculated therapeutic dose at a single administration, to follow this in from four to six hours with a quarter to a third of the total dose, and to give the remainder in a few doses of smaller size at intervals of from four to six hours. By this plan of administration, the full effects can be secured in from twelve to thirty-six hours in the majority of cases.

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The administration of half of the total dose may call for the giving of from 5 to 15 cc. of the tincture at once, and it might be feared that such a large dose might cause gastric irritation and nausea or vomiting. I have given such doses repeatedly since the completion of the greater portion of this work and have never seen the least disturbance of any kind arising as a consequence. This is due to the fact that the nausea and vomiting following the administration of the digitalis bodies is of central origin and results only after the absorption of a sufficient quantity of the drug into the circulation.

It should be reiterated in this place that the use of such large doses of either digitalis or digitoxin as are mentioned is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of the treatment can be graphically recorded at frequent intervals. This practically limits such procedures to hospital practice and to those well versed in the significance of polygraphic and electrocardiographic records.

Certain precautions necessary in using digitoxin according to the calculations he describes are pointed out.

Eggleston (45) has recently published a brief description of his plan for administration of digitalis by the body-weight method, and has given simple formulas for the determination of the dose of the leaf, the tincture and the infusion when the weight of the patient and cat unit strength of the drug is known. The average relative strength of these forms of the drug have been found by Hatcher and Eggleston to be

100 mgm. of the leaf	= 1 cat unit
1 cc. of the tincture	= 1 cat unit
10 cc. of the infusion	= 1 cat unit

When the activity of a particular specimen given is not known, it is safe to use these figures for purposes of calculation; but then only 75 per cent of the calculated dose should be given in order to allow for the possibility of excessive activity of the specimen.

He recommends differentiating urgent and non-urgent cases, and points out the importance of reducing the dose when any member of the digitalis group has been taken in the preceding ten days, particularly when evidences of partial digitalization are present. Eggleston also prescribed certain safeguards which should be carefully followed. The signs of minor digitalis intoxication, such as nausea

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and vomiting, reduction of the heart rate below 60 per minute, and the appearance of frequent premature beats; of definite heart-block; of marked phasic arrhythmia, or of coupled rhythm are to be taken as indications for the cessation of further administration. By the Eggleston method the calculated total amount of the drug may be given to urgent cases in twenty-four or thirty-six hours. By giving an initial dose of the drug consisting of one-third to one-half of the total calculated amount, and then by giving smaller parts of it at six-hour intervals, over-dosage is prevented as digitalis action becomes evident in six hours when the drug is given by mouth.

Eggleston comments on this method of administration as follows:

> The employment of this method of administration of digitalis is without danger to the patient if the directions are followed in detail and if the safeguards are carefully observed. By its employment it is usually possible to produce maximal digitalis action in from twelve to eighteen hours, and marked therapeutic effects are frequently observed within six hours after the initial dose. By its use, it is possible to dispense with the intravenous or intramuscular administration of ouabain, amorphous strophanthin, or other digitalis body in the great majority of cases of heart failure.

The demonstration of the necessity for using digitalis and its allies according to its activity as determined by biological assay is one of the most important results of Eggleston's work, and for that reason, the question of biological assay was taken up quite fully in the earlier part of the review. The relative strength of the various members of the digitalis group were also taken up, and the figures given in that portion of the review may be taken for the determination of dosage for their oral administration. However, the problem of absorption from the gastro-intestinal tract must always be borne in mind, and it will be brought out presently that this has a striking influence on the action of various drugs and preparations when administered orally.

Emphasis should be given to the work of Hatcher (68) on the persistence of the action of the digitalins in connection with dosage. He showed by animal experiments that all the digitalis bodies are synergistic and that the action of one is added to that of another. For this reason, the effect of any drug of this group contraindicates

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the administration of any other of the digitalis bodies. Warning is gravely expressed by Cohn (21) that

> digitalis should, under no circumstances, be given to a patient who has previously been given digitalis in any form or by any route. The failure to obey this warning has, on many occasions, been followed by disastrous results to the patient.

The actual amount of digitalis in terms of the powdered leaf which is usually required to produce the maximum therapeutic results for an average adult weighing about 150 pounds is, according to Eggleston's calculations, 2.25 grams. Mackenzie (109) states that 5 to 8 drachms of the tincture usually produces the desired effects in his cases, an amount which should equal 2 to 3.2 grams of the crude drug. Cohn (20) found that slowing of the heart rate in cases of auricular fibrillation occurred after from 2 to 2.8 grams of the leaf had been given, and Cohn and Fraser (22) found that when the digitalis was administered as the tincture or as digipuratum, a disturbance of the rhythm was usually effected when an equivalent of from 2 to 4 grams of the leaves had been given, although symptoms of intoxication usually appeared before half of this quantity was given.

West and Pratt (156) using a dried aqueous extract of digitalis obtained satisfactory therapeutic effects with a preparation having a cat unit strength of 0.1 gram when from 1.4 to 2.2 grams had been given, while Cohn and Levy (25), obtained the desired therapeutic results when 1 gram of digipuratum of the same activity was given.

White and Morris (159) and Kay (88) have confirmed Eggleston's principles of dosage. Robinson (130) has also administered a standardized tincture in large single doses, calculated according to Eggleston's formula, to 100 cases of heart disease; the doses ranging, as a rule, from 15 to 25 cc. or 15 to 25 cat units, the amount being regulated by the body weight. He observed excellent therapeutic results without encountering any serious toxic effects. He found that the use of large single doses is apparently not dangerous under proper conditions of study, and brings the heart rapidly under the influence of the drug.

Pardee (118) has published the results of a study of sixteen patients to whom the tincture was administered. His results also closely

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confirm the findings of Eggleston. He found wide variations similar to those seen by Eggleston which occur in the amount of the drug required by different individuals to produce the same effects, the variations in his series being from 36 per cent below to 50 per cent above average.

When digitalis is being administered in liquid form it should always be remembered that there is a great difference between the amount contained in a drop and in a minim. Cloetta (19), Pratt (121) Christian (16), Pardee (118), and others have referred to the inadequacy of dosage which has resulted from considering a drop equal to a minim, while in reality, according to Pratt, 1 cc. or 15 minims of the tincture contains 35 to 40 drops when the ordinary medicine dropper is used.

In summing up the work of these several students of digitalis dosage, it may be concluded that the average total amount of the drug necessary to produce therapeutic effects when administered orally has been firmly established, provided the activity of the preparation and the body weight of the patient are taken into consideration. This average total amount may be given in large single doses under proper conditions and when certain precautions are carefully followed, or it may be given in relatively small doses, at regular intervals provided doses are sufficiently large to allow the drug to accumulate in the body and are not below the rate of elimination of the drug, a matter to be considered later.

Pardee (118a) in his second paper on digitalis dosage expresses the opinion that when a tincture of unknown strength is being used, it is safe to follow the rule of giving 1 minim for each pound of body weight in a single dose when the effects of the drug are desired rapidly. This dose is well under the calculated maximun dose of Eggleston, and allows for a considerable increase in the strength of the tincture above that of the average preparation.

The question of applying the body-weight method to children has recently been investigated by McCulloch and Rupe (112). They observed the amounts of the tincture of digitalis necessary to produce definite effects in 36 children varying from one to fifteen years, none of whom had heart disease. Frequent electrocardiograms were obtained and the usual methods of clinical observation were carried

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out. McCulloch and Rupe give the weight of the children in kilograms, but for purpose of comparison with the work already reviewed, it will be given here approximately in pounds, two pounds being allowed for each kilogram. The weights of the children ranged from 17 to 100 pounds.

The tincture employed was standardized at frequent intervals and had continuously a strength of approximately 1 cc. per cat unit. It was found to produce therapeutic effects in adults when given in doses of 0.15 cc. per pound of body weight. In normal children considering the group as a whole, from two to five times as much digitalis per pound of body weight was necessary to produce recognized digitalis effects as was found necessary to produce an optimum therapeutic effect in adult patients with heart disease. The difference of children in this regard was especially true for those weighing over 40 pounds. There were 12 such cases in the series, 8 of whom showed no response to doses of 0.29 to 0.48 cc. per pound, while the other 4 required from 0.62 to 0.87 per pound of body weight before showing evidence of the action of the drug.

Among the 24 children weighing less than 40 pounds, 14 responded to less than 0.5 cc. per pound while 8 required from 0.5 to 0.87 cc. per pound.

Two children aged twelve and twenty-one months respectively weighing 19 pounds each did not respond to the drug until 19.2 cc. had been given in 24 doses, requiring approximately 1 cc. per pound of body weight before showing evidence of digitalis action. The total amount of the tincture was given in this series in from 5 to 24 doses, being administered 4 times a day. Elimination therefore probably had little or no influence on the total amount taken, although of course absorption is a factor difficult to evaluate.

McCulloch and Rupe conclude that children weighing from 16 to 40 pounds, or up to about the age of four years, respond more readily as a rule to digitalis, than do those above this weight and age while the older children required a distinctly larger amount per unit of body weight than is required to produce comparable effects in adults with heart disease. Considerable variation in the amount of the tincture necessary to bring about a response in the hearts of the children was found, but it is evident that relatively large doses of digitalis

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can be administered to children with comparative impunity. McCullock and Rupe (112a) have studied a second series composed of children with heart disease. In this series they found no qualitative difference in the effect of digitalis when compared to the action of the drug on adults. They found, however, that children with heart disease require about 50 per cent more of the drug per pound of body weight on an average than do adults to obtain the same results. Some of the cases required 100 per cent more of the drug, that is a quantity double the estimated dose, while others required only 10 per cent additional amount.

b. Absorption of digitalis from the alimentary tract is a problem which has an important bearing on the dosage of the drug when administered by mouth, and has recently received considerable attention. The relative rates of absorption of the various members of the digitalis group, variations in absorption of a single preparation and influences delaying absorption have been studied both in the laboratory and in the clinic.

Schmiedeberg (139) states that the active principles of digitalis, digitoxin, digitalin and digitalein are slowly absorbed from the gastro-intestinal tract.

Ogawa (116) called attention to the delay in the time required for digitalis to affect the heart when given by mouth as compared with the time required after intravenous injection. He concluded that the slowness of absorption is the greatest factor in the "latent period" of digitalis action. He states that digitoxin is not absorbed from the stomach and only with relative slowness from the intestines. He found that by examining the withdrawn gastric contents that different preparations of digitalis have different rates of absorption, and that digitoxin for which he applied a colorimetric test, remains for a shorter period in the stomach when taken as digipuratum than when taken as powdered leaves or as the infusion.

Ogawa is of the opinion that the absorption of the digitalis bodies is further delayed by congestion of the abdominal vessels, as he found that experimental obstruction to the portal circulation prevented their absorption. Cloetta (19) also considers that congestion of the intestinal vessels and of the liver interferes with the absorption of digitalis. Eggleston (42) on the other hand, states that prompt and

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efficient absorption of digitalis and digitoxin seems to take place even in the face of considerable abnormality of the alimentary canal, for patients manifesting evidence of marked congestion of this region, resulting even in repeated vomiting, respond quite as promptly and to the same doses as do those who are apparently free from disturbance.

Haskell, McCants and Gardner (66) studied the relative rate of absorption of various digitalis bodies from the gastro-intestinal tract of animals. They determined the amount of digitalis intravenously injected necessary to produce emesis after constant amounts had been given orally, and took as the measure of absorption from the gastro-intestinal trace the size of the intravenous dose necessary to produce this result, as the larger the amount absorbed from the gastro-intestinal tract, the less is needed by vein. They found that the tincture of digitalis was much better absorbed than the infusion, and that the expensive preparations, digipuratum, digalen and digipoten had no advantages over the tincture in regard to absorbability.

The most important work that has been done on the matter of absorption is that from the laboratory of Hatcher and from the clinic of Eggleston. Their numerous papers contain many references to this matter. Hatcher and Baily (61) called attention to the fact that the tincture of strophanthus is poorly absorbed from the gastro-intestinal tract, and Eggleston has recently stated in discussing the work of White, Balboni and Viko (158) which has already been referred to, that the tincture of squill owes its relative inactivity to its poor absorption. Hatcher and Bailey (73) have also pointed out that dangerous variations in absorption of strophanthus may take place. Eggleston (47) has recently summarized his ideas regarding the use of members of the group other than digitalis as follows:

> The materia medica of the digitalis group of drugs is large, but digitalis alone is well absorbed from the alimentary tract of man. Strophanthus, convallaria, squills, etc., are alike poorly absorbed and irregularly absorbed. Strophanthus deserves special mention, because it is 100 times as active as digitalis, yet the official dose is only half that of digitalis, and it is often given in equal doses. The irregularity of its absorption is of greater importance than the fact that its absorption is generally poor, for in some cases, serious poisoning has resulted from the rapid absorption of the customary dose. We are convinced that strophanthus should never be

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used for oral administration to man on account of the danger of serious accident, despite the fact that it often has been so used with satisfactory results.

J. T. Halsey (62) has expressed similar views regarding the oral administration of strophanthus, and contends earnestly that the poor and irregular absorbability of strophanthus from the alimentary canal should prohibit its use by mouth.

Recent interest has centered largely on the absorbability of the tincture of digitalis, the most widely used form of the drug. Many references are found in the older literature regarding the slow absorption of the drug in any form, but the recent clinical studies furnish definite facts regarding the absorption of digitalis from the gastro-intestinal tract in man. Eggleston (47) states that the absorption of a single dose of a high grade tincture is apparently completed in six hours and he quotes the results of Pardee and of Levy, both of whom obtained electrocardiographic evidence of digitalis action in from two to four hours after the drug was given by mouth. Robinson (129) administered large single doses to 26 patients with auricular fibrillation and observed the onset of ventricular slowing constantly in from 2 to 5 hour after the administration of the drug. These findings indicate that with the tincture he used a fairly rapid and uniform rate of absorption took place from the alimentary tract.

Pardee (118a) has studied the rate of absorption of digitalis from the gastro-intestinal tract. He gave the drug in the form of the tincture in doses determined by allowing 1 minim for each pound of body weight, and administered this amount in a single dose. He then followed the action of the drug in frequently taken electrocardiograms, noting especially variations in the T wave and in the heart rate. Changes in the T waves indicative of digitalis action were observed within two hours of taking the drug in three of nine patients, while within three hours, these changes were observed in seven of the nine patients. Pardee's observations are confirmatory of those of Robinson, although the doses used by the former were considerably smaller. Pardee considers that the variation in the size of the dose within certain limits does not appear to have a marked influence on the time of onset of the digitalis action.

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Eggleston (42), has compared the absorption of the tincture of digitalis with that of digitoxin, digitalin and digitalein. The last two substances are so poorly absorbed from the alimentary canal as to render them unsuitable for therapeutic use, while the absorption of digitoxin is slightly less rapid than that of the tincture.

Attention has been directed recently, however, to marked variations in dosage required to produce well defined digitalis action when tinctures carefully assayed by the cat method were used. Wedd (152) found that in one patient 100 cc. of a standardized tincture produced no effect while six months later definite digitalis action followed the administration of 35 cc. of another equally active tincture. Of the first tincture 280 cc. were given to another patient during a period of ten weeks and produced no clinical symptoms. He found that from 24 to 34 cc. of the first tincture were required to cause inversion of the T wave of the electrocardiogram while it occurred with 10 cc. or less of the second equally active tincture. Wedd attributes this difference in the action of the two tinctures to variations in absorption, and says that it is evident that biological standardization is no guarantee of the clinical efficiency of a given preparation of the drug.

A similar experience occurred to Oppenheimer (quoted by Eggleston (46)), who gave 5 to 9 times the usual dose of the tincture without evidences of either therapeutic or toxic action. Although individual susceptibility may play some rôle in producing these marked discrepancies, the variations in absorption seem to be the prime factor.

Hatcher (71) has taken cognizance of these variations in digitalis action, the frequency of which is not yet known, and has investigated them. He says that

> Certain of the digitalis principles are readily absorbable from the gastrointestinal tract of man, as well as that of animals, while others are absorbed much less readily, and it seems probable that the failures just mentioned arose from the fact that preparations contained relatively large proportions of the less readily absorbable active principles.

Hatcher has found that the more readily absorbable principles are soluble in chloroform, and he describes a method for separating the chloroform soluble from the chloroform-insoluble principles. He has

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obtained a chloroform-soluble substance resembling somewhat digitoxin, both chemically and pharmacologically. It may be dissolved in alcohol and is miscible with water without precipitation. The resulting weak alcoholic solution has been found to undergo little change during a period of a year since it has been under observation. This preparation seems to exert the typical cardiac action of digitalis, and has all its other advantages.

The clinical use and especially the absorbability by patients of this preparation has been studied by Eggleston (46) who has published some preliminary observations. He shows the marked uniformity of absorption of the chloroform-soluble extract of digitalis prepared from a variety of different leaves. This uniformity contrasts sharply with the variations noted in the use of certain tinctures from a variety of sources.

The chloroform-soluble extract is shown to be absorbed at least as rapidly as the best tincture of digitalis, and its persistence of action is apparently of the same order as that of digitalis of the best grade. The observations indicate that for oral administration the chloroform-soluble extract is not superior to a well absorbed tincture of digitalis, but it is far superior to tinctures which are derived from a variety of sources, the absorption of which shows very marked variations when individual specimens are compared. The chloroform-insoluble extract is very poorly absorbed from the human alimentary tract as well as from that of the cat.

It is evident that absorption must be taken into more strict account than it has been in the past in determining the efficiency of a digitalis preparation, and means must be devised if possible to determine its absorbability as well as its activity in the standardization of the digitalis intended for oral administration.

The effect of the gastro-intestinal secretions on the digitalis bodies is a problem closely allied to that of absorption. Ogawa (116) studied this problem in animals and in man, and found that strophanthin was destroyed by the gastric ferments, just as Holste (quoted by Ogawa) concluded that the pancreatic secretion destroyed digitalin. Ogawa's study revealed, however, that the glucosides of the digitoxin fraction are resistant for several hours to the juices of the gastro-intestinal tract.

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Cloetta (19) has investigated the effect of gastric juice on digitalis in vitro, his digalen preparation being subjected to shaking for one hour at 38°C. with varying percentages of hydrochloric acid. The percentage of the drug destroyed was then determined and the following results were obtained:

with 22 per cent HCL	100 per cent digalen destroyed
with 12 per cent HCL	60 per cent digalen destroyed
with 4 per cent HCL	40 per cent digalen destroyed
with 3 per cent HCL	35 per cent digalen destroyed
with 2.5 per cent HCL	35 per cent digalen destroyed
with 1.5 per cent HCL	25 per cent digalen destroyed

Cloetta considers that a "nerve poison" is generated by the action of hydrochloric acid on digitalis, the therapeutic properties of which are destroyed. He recommends giving the drug when the stomach is empty, and giving it with an alkaline mineral water, weak tea or a mucilage. He also believes that his findings indicate the usefulness of giving digitalis by rectum, which he advocates. Further study of these subjects is needed before they can be adopted as principles influencing the therapeutic use of digitalis.

The problem of the decomposition of various digitalis bodies by acids and digestive ferments has been discussed by Hatcher and Eggleston (78) in their studies in elimination, and a review of a number of experimental studies of this subject is given, including that of Holste quoted by Ogawa. Following their analysis of these various investigations, they say that there is no convincing evidence that any of the digestive juices or their ferments have any important destructive action on any of the digitalis glucosides following their therapeutic administration by the mouth.

c. The speed of action or time elapsing between the oral administration of digitalis and the appearance of its effects is also a matter on which absorption has an important bearing. The fact that digitalis requires many hours or even days to affect the heart when given in the customary doses has been perhaps the chief disadvantage in the use of the drug in cases of heart disease in which prompt action is urgently indicated.

Cushny has stated that one great limitation in the use of digitalis is caused by the slowness with which its action is elicited. "Rarely

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is any distinct change to be seen before the fourth day of treatment, and this precludes its use in the most acute cases." (Quoted by Eggleston (42)). Recent clinical studies have shown, however, that it is the size of the dose rather than the delay in the absorption or in the action of the digitalis that is the most important factor in regulating the speed of action of the drug. It is necessary for a certain amount of the drug to be present in the body before the action appears, and the action appears much more quickly with large than with small doses, several or many of which are needed to supply the amount of the drug necessary to exert its action. It has been the time required for the accumulation of a sufficient amount of digitalis that has become largely responsible for the ideas regarding the very slow speed at which the drug exerts its action.

Eggleston (42) has shown the relation between dosage and speed of action for digitalis and digitoxin, large doses of the digitalis bodies becoming active on an average in 13 hours; small doses in thirty-eight hours while large doses of digitoxin required fifteen hours to produce their earliest effect, and smaller doses required forty-two hours. He demonstrates that both these drugs when given in large doses can induce full therapeutic effects within comparatively few hours after the administration of the first dose.

Robinson (129) has investigated the question of the rapidity of the action of digitalis by giving the full calculated amount of the tincture in a single dose to patients with auricular fibrillation. In a series of patients in whom digitalis caused a striking reduction of the ventricular rate, he found that ventricular slowing (or disappearance of auricular flutter) began in from two to five hours, in all of the 16 cases where the initial effect was observed, and that maximum slowing in 26 cases occurred in from six to twenty-six hours. As only one dose was given in most of these cases, the question of the accumulation of the drug played no part.

These results have been confirmed by Eggleston (46) and by Pardee (118a), who found that two or three hours after a single large dose of the tincture slight changes in the T wave of the electrocardiogram characteristic of digitalis action usually appeared. Eggleston also quotes Scott as having obtained digitalis effects in from one to two hours by the administration of 10 cc. of the chloroform-soluble extract of digitalis given in a single dose.

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Cohn and Levy (25) have compared the speed of action of comparable doses of digitalis (digipuratum) when given by mouth and g-strophanthin when injected intravenously. An effect with digitalis has been observed in a little more than two hours, while the speed of action is often faster with strophanthin than with digitalis, though when strophanthin is given in divided doses it may require nearly two hours to obtain an effect. In other instances, an effect may be obtained, as is well known, in twenty minutes or less.

This matter of speed of action of digitalis has been recently summed up in a vigorous way by Hatcher (70).

It is necessary to call attention again to the difference between an immediate action and immediate effect, because it has long been taught, without a particle of real evidence, that the action of digitalis cannot be induced promptly. The whole range of digitalis action up to the maximum, that is, cardiac stoppage, can be induced in from five to fifteen seconds by the intravenous injection of digitalis tincture deprived of its alcohol, or digitoxin. This simple experiment disposes forever of the mischievous claim that digitalis action is slow. The *effect* of therapeutic doses is *gradually* induced; the action is *immediate*. A bullet fired through the heart *acts* instantaneously; the *effect* is a fatal hemorrhage, the rapidity of which depends largely on the size of the wound. With suitable dosage, digitalis exerts its action in much less time than was formerly believed to be possible.

2. Intravenous administration

The value of the intravenous administration of ouabain, strophanthin, and some other principles of this group is generally recognized, and it is considered a life-saving measure because of the promptness with which the action of these drugs can be obtained in urgent cases of heart failure. In emergencies, however, the cause of heart failure may be difficult to determine and when it occurs under such conditions as during a surgical operation, its cause is often incorrectly attributed to "cardiac dilatation," as Levine has recently pointed out. The use of large doses of digitalis by mouth and the prompt action which usually results makes the use of these drugs by intravenous injections rarely necessary. It must always be employed with caution, as has been pointed out in discussing fatalities following its use, and intravenous injections should never be given to

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patients who have been receiving full doses of the digitalis bodies in any form.

Digalen, the so called soluble digitoxin, prepared by Cloetta (17) is the first form of digitalis recommended for intravenous employment. Edens (36) was among the first to report favorable results with the intravenous administration of this drug, and he emphasizes especially the rapid action thus obtained, and the fact that the drug can be used in cases where absorption from the gastro-intestinal tract would probably be distinctly faulty. He considers its use not without danger, however, and recommends its use by slow injection in desperate cases. Cloetta (19) has recently expressed his belief in the intravenous use of digalen as the ideal method of giving digitalis.

Strophanthin was introduced as a drug for intravenous administration by Fraenkel, and its use is fully discussed by Fraenkel and Schwartz (54). They recommended a dose of 1 mgm. ($\frac{1}{65}$ of a grain) but say it should not be given more often than once a day. Agassiz (2), studied the effect of intravenous injections of strophanthin on a series of cases of auricular fibrillation and recommends doses of $\frac{1}{125}$ to $\frac{1}{65}$ grain repeated several times every one to three hours for several doses. Ventricular slowing usually resulted from one injection. It may appear as early as half an hour after the injection, but the ventricular rate may continue to be further slowed during the following twenty-four hours. Two or three injections are usually sufficient to produce the normal ventricular rate in 4 to 9 hours. Strophanthin employed intravenously seemed to possess action quite similar to the other members of the digitalis series. Agassiz found the most suitable method of administration to consist in the injection of $\frac{1}{125}$ grain repeated after three hours, and followed after a further interval of three hours by an injection of $\frac{1}{65}$ grain if required. The injection may be followed by pain at the site of injection and by a rise of temperature. In one instance, a patient died unexpectedly some twelve hours after the injection had ceased, but the relation of cause and effect was not definitely established.

Fulton (156) reports a case of auricular fibrillation treated by intravenous strophanthin in which the pulse reduced from 144 to 34 within a period of about twenty-four hours, after two doses had been given, the first of $\frac{1}{125}$ of a grain and the second of $\frac{1}{125}$ of a grain.

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The condition of the patient passed quickly from one of extreme discomfort with dyspnea and restlessness to a condition of perfect comfort.

Such observations as those of Agassiz and Fulton indicate that doses of 1 mgm. ($\frac{1}{60}$ grain) as advocated by Fraenkel are too large, and fatal accidents have resulted from the use of strophanthin in such doses, as has been brought out when digitalis fatalities were discussed. However, the work of Levine and Cunningham (94) indicates that it is no more dangerous than digitalis intravenously administered when the so-called margin of safety is considered, the average difference between the minimum lethal dose and the minimum toxic dose being 48 per cent in each instance. They have also found that various digitalis preparations act as quickly on the heart when injected into the veins as does strophanthin. They observed toxic effects two minutes after the intravenous injection of digitalis and cardiac standstill in sixteen minutes. All effects produced by either digitalis or strophanthin were seen to occur within six minutes after the injections.

Levine (92) has suggested a fractional method of intravenous injection of strophanthin on the basis of his experimental studies of the action of the drug on the living cat's heart. He points out that numerous fatalities have resulted from the intravenous administration of strophanthin, but most of them have occurred when the drug was given to patients who recently had taken digitalis, or when large doses were repeated on the same day. His experiments show that it is practically impossible to foretell the toxic dose for patients but they indicate that a "margin of safety" exists between the minimum lethal dose and the minimum toxic dose. Levine recommends that strophanthin be injected in several fractions of the desired dose, a half hour intervening between the fractions, during which time, the signs of intoxication are watched for. This procedure will prevent giving more than one fraction, say 0.1 mgm. in excess of the amount necessary to produce the earliest toxic signs. Electrocardiograms are very useful in showing premature beats or changes in the P-R interval as a result of the drug. This procedure should certainly diminish or avoid the dangers of the drug. According to Levine, Vaquez and Lutembacher have reported almost 2000 intravenous injections of ouabain without harm or fatality.

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Danielopolu (34a) has also recently stated that strophanthin can be safely given only in small doses, and recommends the use of 0.25 mgm. intravenously two or three times a day. This he calls the method of fractional doses, and says that by observing the patient carefully before each dose, the drug can be given to patients with extreme myocardial derangement or with kidney disease, which are to be taken as contraindications when larger doses are employed.

Cohn and Levy (25) report that the g-strophanthin which they have used in their comparison with digitalis had an average cat unit of 0.104 mgm. and was given usually in two doses at an interval of one hour—the first of from 0.4 to 0.5 mgm., and the second from 0.3 to 0.5 mgm. No serious untoward effects were observed after these doses.

The drug produced premature beats and ventricular ectopic tachycardia in 52 per cent of the cases of auricular fibrillation and 12.5 per cent of the cases with normal hearts. These toxic effects always appeared within twenty minutes after the injection causing them and disappeared within eight hours. Nausea and vomiting were noted in 10 per cent of the cases. Comparable doses of digitalis by mouth caused undesirable effects in a much smaller percentage.

An important indication for the intravenous use of a digitalis body is persistent vomiting which may be associated with heart-failure as, under such circumstances, it may be impossible to administer the drug orally. Under these circumstances, strophanthin had best be used, for although other digitalis bodies have been employed intravenously, they have not as yet been placed upon as sound a basis for this purpose as strophanthin.

3. Subcutaneous and intramuscular administration

Subcutaneous and intramuscular administration has not proved desirable, and it has not been employed in any of the recent studies of digitalis. Several preparations have been recommended as suitable for subcutaneous and especially intramuscular injections, but all are decidedly painful and apt to cause necrosis, and their dosage has not been accurately determined. Hatcher and Eggleston state emphatically as a conclusion from their studies on the absorption of drugs in general that no rule can be formulated for the calculation of the ap-

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propriate dose by one mode of administration from the dose by any other mode of administration. Such determination can be made only be experiment.

4. Rectal administration

Rectal administration has been recommended by Eichhorst (49) in the treatment of chronic myocardial insufficiency. He described several cases which were not benefited by the usual drugs and which did not respond favorably to three powders a day composed of 0.1 gram of powdered digitalis, 1 gram of diuretin and 0.5 gram of saccharin. These cases showed beneficial results from small daily enemata containing 10 drops digalen (Cloetta), 10 drops of the tincture of strophanthus, 0.3 gram of theocin and 5 cc. of lukewarm water. This prescription was injected daily into the bowel and retained. Eichhorst has continued their use over periods of years without difficulty. Five to ten drops of the tincture of opium is added when there is pain or difficulty in retaining the enemata. Eichhorst states that very striking results were obtained by the use of such enemata.

Cloetta (19), has commented upon Eichhorst's results, and he is favorably disposed toward the method. He believes that one advantage of rectal administration is that it does not subject the drug to the action of the gastric juice, which his experiments indicate may destroy it. He believes the favorable results that have been reported are accounted for also by the fact that some of the veins leading from the rectum, the inferior and part of the middle hemorrhoidal veins, empty directly into the inferior vena cava, and do not send the blood through the liver. Because of this, some of the drug introduced into the rectum would probably reach the heart without going through the liver, where it may be destroyed.

The rectal administration has not been extensively used, but it deserves further study, and more should be known regarding the action of the digitalis bodies when introduced into the body by this route.

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XII. PERSISTENCE OF ACTION

It has long been known that the action of digitalis persists after the drug is discontinued. Withering (163) recognized this fact in regard to nausea and vomiting, and recommended that the drug be stopped as soon as its activity became manifest, inferring that its beneficial effects persist thereafter. A number of problems are involved in the persistence of action of digitalis. Absorption, fixation by the tissues and especially the destruction or elimination of the drug from the body, may all play some part in determining the continued action of the drug, and as there is but little known regarding any of these matters, no satisfactory explanation of the fundamental problem can be offered.

A number of clinical observations have been made with exact objective methods which show the length of time patients remain under the influence of the drug after full digitalization has been accomplished and the drug withdrawn. Bastedo (5) observed the continuation of digitalis heart-block for three and a half weeks after the withdrawal of the drug. Cohn (20) found by means of electrocardiograms that delayed conduction always persisted for two days in relatively healthy hearts and exceptionally for two weeks after the discontinuance of digitalis, while Cohn, Fraser and Jamieson (23) observed the persistence of the T wave changes in the electrocardiogram for from five to twenty-two days after the drug was stopped.

Eggleston (39) has studied the relative duration of various cardiac manifestations of digitalis action in fifteen cases of his own and from the literature. Coupled beats persisted from four to twelve days, heart block three to six days, combined phenomena six days, auricular fibrillation three days, extrasystoles and sinus arrhythmia two days. Conclusions regarding the relation of digitalis and the disappearance of transient auricular fibrillation is hardly justified.

Robinson (129) followed the ventricular rate of a number of cases of auricular fibrillation after it has been slowed by large single doses of the tincture of digitalis. In twelve cases which were carefully controlled, the ventricular rate began to accelerate in from four to fifteen days after the administration of the dose of digitalis which had caused marked slowing. This acceleration was taken as evidence

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that the heart had ceased to be under the action of the drug. The drug was active on an average, for nine days and six hours in these cases. Kay (88) has reported ventricular slowing in auricular fibrillation for from three to five days after doses of digitalis given by the "Eggleston method."

It is evident that various manifestations of digitalis action persist after the drug is withdrawn for from two to twelve days in most cases, but may persist for three weeks or more.

The action of strophanthin when administered by vein has been found by Agassiz (2) to retard the rate of the ventricles of cases of auricular fibrillation for two or three days, when acceleration begins, and the original rate, present before treatment, is seen again in about one week.

Cohn and Levy (25) have compared the persistence of action of digitalis (digipuratum) and g-strophanthin given in comparable doses to cases of auricular fibrillation and found that while the digitalis effect endures usually beyond ten days, and has lasted as long as twenty-three days, it is rare for strophanthin to keep the ventricular rate low for more than five days. It did so once for nine days, however.

A question closely allied with the persistence of action is the so called *cumulative action* of digitalis. Eggleston (39) has discussed the term "cumulative," which is a very loose one. It is generally taken to express the development of signs of action during the administration of small repeated doses of a drug which are much more marked than those caused by a single small dose. Toxic symptoms are usually implied. Accepting this definition, the cumulative action in the case of digitalis is simply the result of a summation of amounts absorbed and active in the body when the intake of the drug is greater than its elimination. The continued use of small doses of the drug raises by the process of summation, the total amount of the drug active in the body, and perhaps fixed by the heart or the nervous tissues to such a point that toxic symptoms develop. When the persistence of action of digitalis is borne in mind the fear of its so called cumulative action can be put aside.

Hatcher (68) has investigated the persistence of the digitalins by means of animal experiments, especially with the hope of throwing

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some light on the cumulative action of the drug, which generally means, he says, action which is manifested rather suddenly after the continued use of doses which singly do not cause perceptible effects. The method he employed was as follows: The fatal dose of the digitalis body for a given species was determined in a series of experiments. After toxic, but sublethal doses of the drug had been given, the animals were kept under observation for periods of one to thirty days, and then the percentage of the standard fatal dose required to kill in a characteristic way was determined. The decrease in the amount necessary to produce a fatal result was taken to represent the amount of the drug remaining in the body of the animal. Hatcher and Brody (74) had previously shown that the various digitalis bodies are synergistic, and that ouabain was capable of replacing the various digitalins in the estimation of the fatal dose, and this drug was generally employed for the second injection. Cats were found to be the most useful laboratory animal for this purpose. The many experiments will not be reviewed. Certain conclusions are of importance from the point of view of the therapeutic use of digitalis. Hatcher says that the production of the phenomena commonly called "cumulative action" of the digatalins depends on the relationships existing among a number of factors, including absorption, elimination, and persistence of action, all of which are in need of investigation. The use of the term cumulation tends to perpetuate a misconception. The action of the digitalis persists for periods of time which vary widely with different members of the group, the action of digitalis and digitoxin persisting much longer than those of the other digitalins in common use. The cardiac action of a single very large intravenous dose of digitalis or digitoxin may persist for a full month in the cat, while similar doses of digitalin, ouabain or strophanthus persist for only a day or at most a few days.

Careful regulation of the therapeutic dosage of the digitalins is necessary in order to avoid accidents. This is especially necessary when they are used in such a way that the action is elicited promptly during the period when the action of a previously used digitalin persists, and in this connection it must be remembered that every digitalin is a synergist of every other member of the group.

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XIII. ELIMINATION OF DIGITALIS

Little is known and relatively little has been thought apparently regarding the matter of the ultimate fate of digitalis in the body, its destruction and its elimination. It is a matter of real importance, however, in the therapeutic employment of digitalis, when frequent doses of the drug are being given, and especially when it is desirable to keep a patient constantly under the influence of the drug without producing toxic symptoms. This is apparent from the foregoing discussion of the "cumulative action" of the drugs of the digitalis group.

Schmoll (141) recommends that 0.1 gram of digitalis be given daily to heart cases in order to take advantage of what he calls the tonic use of the drug, and he says this dose causes no toxic effects because it is the amount of the drug which can be excreted daily.

The rate of disappearance from the body has been the subject of a clinical investigation by Pardee (118). He points out that when digitalis is given for the purpose of keeping a patient constantly under its influence, improper dosage makes the patient liable to pass gradually out from under the influence when too small a dose is given, or with over-administration, leads to toxic symptoms. As animal experiments cannot give a definite answer as to the rate of disappearance of the drug from the human body, Pardee investigated the question directly in patients by the following method. The tincture of digitalis was given until mild toxic symptoms appeared, when it was stopped entirely for a number of days. It was then given again until the same toxic symptoms reappeared. The difference between the amount of the drug used in the second and in the first course, divided by the number of days between the two toxic points, is taken to indicate the daily average amount of the drug that had disappeared from the body in the interval. It is assumed that there is no change in the patient's tolerance for the drug, a fair assumption in the light of the results with repeated courses in the same patients. The initial doses were so arranged that toxic symptoms appeared in from two to six or eight days; while the second course was usually complete in an average of five days, although it was sometimes prolonged.

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Vomiting was the usual toxic symptom employed. Twenty-two tests were carried out on 16 cases, all of whom had a rather marked degree of heart failure before the initial course, but were in better condition when the second course was given. A standardized tincture having a strength of 1.25 cc. per cat unit was used.

The method employed by Pardee showed an average daily rate of disappearance of the drug from the body of 22 minims of the tincture. In half the cases the amount was below and in half above the average, the maximum variations being from 55 per cent below to 82 per cent above. The results of this investigation resemble other work on digitalis in the variability of figures, but in 18 of the 22 tests, the results lay between 12.3 and 30.6 minims per day; while in eleven tests, half of the total, it was between 13.3 and 27 minims, the latter a total variation of only 62 per cent. Pardee says:

> It is evident from this that the average figure of 22 minims per day would afford a fairly satisfactory basis for long continued digitalis medication, since in only half of the cases would it be much more or much less than the patient's ability to dispose of the drug. These results demonstrate the reason for the approximate efficiency of a dose of ten minims of the tincture twice a day, which has commonly been considered sufficient to maintain constantly the digitalis effect. They also demonstrate a new phase of the variability from one individual to another, in the action of digitalis, a variability in the rate of disappearance from the body.

It is interesting that Schmoll's figure of 0.1 gram of digitalis which is equal to about 15 minims of the tincture recommended a number of years ago, should approximate Pardee's figure fairly closely. The importance of this subject warrants its further clinical investigation.

Hatcher and Eggleston (78) have recently published extensive studies in the elimination of certain of the digitalis bodies from the animal organism. Their review of the literature shows that the subject is in an unsatisfactory state. Their studies deal mostly with the elimination of various pure digitalis bodies in the rat, while the elimination of ouabain in the cat and dog was also investigated.

Ouabain disappears rapidly from the blood following injection, and seems to be taken up by the liver where it is apparently decomposed.

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Both destruction in the body and elimination by the kidneys probably occur. Many points regarding the elimination of the digitalis bodies remain to be settled, and this work of Hatcher and Eggleston does not appear to present any facts which can be applied directly to the therapeutic use of digitalis.

XIV. PREPARATIONS OF DIGITALIS AND ITS ALLIES

The number of digitalis preparations is very great and they have been shown to vary greatly in activity. It is hardly worth while to attempt a description and criticism of the many proprietary preparations. It seems more desirable to attempt to review the rules by which the useful preparations can be distinguished from the less valuable. Of course activity as established by a reliable form of biological assay, preferably the cat method of Hatcher and Brody (74) is essential.

The cost and recently the availability, especially of foreign products are to be considered even when the medicinal qualities are satisfactory. As Eggleston (47) has recently stated:

> Of the many proprietary preparations and specialities which are offered with high claims for oral administration, none is superior to the powdered leaf or a tincture of high grade, and most are decidedly inferior. All are quite costly and the price of some is exorbitant. If one feels impelled to employ one of these, digipuratum or digipoten will be found to be the best, but these are merely carefully assayed, purified preparations from good digitalis leaves.

The dried aqueous extract recently described by West and Pratt (156) at first seemed to be an excellent preparation but has since proved too hydroscopic. It was used by them in capsules containing 0.1 gram. The chloroform-soluble extract which Hatcher (71) has obtained has been successfully employed by Eggleston (46), and may prove to be superior to the ordinary tincture, on account of its uniformity of absorption.

The infusion of digitalis has no advantage over the tincture or powdered leaves, and the large amount necessary for proper dosage make it less desirable.

Weiss and Hatcher (54a) have recently investigated the relative merits of the infusion and the tincture once more. They found that

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the infusion of digitalis prepared according to the method prescribed in the United States Pharmacopoeia does not represent the drug completely, so that its strength cannot be determined from that of the leaf from which it was made. They give a method by which all water-soluble active principles can be obtained. They show that the full strength of the drug is represented by the tincture, and neither the infusion nor the tincture contain amounts of the saponin bodies sufficient to cause undesired effects. Weiss and Hatcher point out that they can find no evidence of any qualitative difference between the actions of the tincture and those of the infusion. The common belief that the infusion deteriorates rapidly is apparently much exaggerated, because Weiss and Hatcher report that an infusion prepared by the method they recommend, kept in hermetically sealed bottles for two years and five months retained its activity unimpaired, as shown by tests on cats and by its therapeutic results. A properly prepared and preserved infusion would seem therefore to have a usefulness quite similar to that of a good high grade tincture.

None of the preparations claiming to be devoid of effects on the gastro-intestinal tract should be used on that account. The absence of this effect must be viewed as evidence of inactivity, because of lack of potency or poor absorption, and if gastric symptoms are not produced, the desirable effects can not be expected.

Strophanthus and squills as well as most of the purer derivatives of digitalis are so poorly and irregularly absorbed from the gastro-intestinal tract that they should never be used for oral administration. Crystalline g-strophanthin is the most satisfactory drug for intravenous use provided it is protected against deterioration by regulation of its reaction and by its being marketed in hard glass containers. The importance of this has been shown by Levy and Cullen (95).

The French preparations, Arnaud's ouabain and Nativelle's crystallized digitaline have been assayed by Levine (93), using the cat method, and he found that this ouabain had a cat unit of 0.059 mgm. It is nearly twice as active as the ouabain used in America, which Hatcher has shown to have a constant unit of 0.1 mgm. Nativelle's crystalline digitalin in sterile oil capsules had a cat unit of 0.86 mgm., the tablets of 0.71 mgm. Levine suggests that the dose of 0.25 mgm. of digitalin advised by the manufacturers is too small

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for good therapeutic effects. Perhaps the sterile oil preparation is the most satisfactory for intramuscular injection if such use of the drug be found necessary. It was stated, when the so called digitalis group of drugs was discussed as a whole, that this review would deal almost exclusively with digitalis and strophanthus. Recently three other members of the group, squill, apocynum and convallaria have been investigated from the point of view of their therapeutic effects by White and his collaborators. As their therapeutic value has been compared with that of digitalis, a brief statement may be made regarding their use in the treatment of heart disease. The digitalis-like action of squill was studied in fourteen patients by White, Balboni and Viko (158). Thirteen of their cases showed auricular fibrillation, most of which had been previously shown to respond well to digitalis. They found that ventricular slowing and the characteristic changes in electrocardiograms were produced by the drug, indicating that squill does have a definite digitalis-like action, but only when doses much larger than those usually recommended were given. They administered the tincture of squill, and found that from 8 to 16 cc. were necessary at each dose instead of the recommended dose of 1 cc. (15 minims). No definite diuretic effect could be attributed to the action of the drug. Eggleston, as previously mentioned, stated in discussing this paper that in his opinion the large doses were necessary on account of the poor absorption of the drug from the gastro-intestinal tract. He further says that he can see no reason for using squill in place of digitalis in the treatment of heart disease.

Apocynum and convallaria have been similarly studied by Marvin and White (110a). Apocynum was administered by mouth in the form of the fluid extract to twelve patients. Although the drug was found to have an action similar to digitalis when given to patients with auricular fibrillation, it produced pronounced gastro-intestinal symptoms, which occurred with the smallest doses that had any demonstrable effect on the heart. Its persistence of action was transient, lasting only twenty-four to forty-eight hours. The drug was much less effective in doses that could be given than digitalis in the treatment of heart disease. Convallaria was also given to twelve patients in the form of the fluid extract. It was found to be distinctly less efficacious than digitalis, causing clinical improvement in only two of

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the twelve cases. Nausea and vomiting occurred in nine and diarrhoea in six cases. Its action was transient. Marvin and White conclude that

it would seem from our results that neither apocynum nor convallaria can be substituted for digitalis. In our experience digitalis has been characterized by quicker action, more pronounced effects, less discomfort, and more prolonged improvement, than are seen following either of the other drugs. We are convinced that both these members of the digitalis series have no place in the rational treatment of heart failure.

In spite of the fact that these studies bring out, apocynum and convallaria are used to a considerable extent, as two American pharmaceutical companies reported to Marvin that their annual sales amounted to about 15,000 pints.

In the therapeutic use of digitalis certain requirements should be insisted upon by the medical profession. All products put upon the market should be labelled not only with the results of the biological assay, but also with the date of manufacture and of the assay. The dose should be indicated according to the actual strength of that particular preparation. When the medical profession learns to regulate the dosage of the digitalis bodies properly, and to understand thoroughly the indications for their use, the great value of this group of drugs in the treatment of heart-failure will be more generally appreciated even than it is at present. The selection of the form in which the drug is used is relatively unimportant if activity and especially dosage are properly controlled, and if the use of the unsuitable members of the digitalis group is avoided.

REFERENCES

(1) Abel and Macht: The poisons of the tropical toad, Bufo agua. Jour. Amer. Med. Assn., 1911, lvi, 1531.

(2) Agassiz: Observations upon the effects of strophanthin in cases of auricular fibrillation. Heart, 1912, iii, 353.

(3) Bachmann: Complete auriculo-ventricular dissociation without syncopal or epileptiform attacks. Amer. Jour. Med. Sc. 1909, cxxxvii, 342.

(4) Bachmann: Sphygmographic study of a case of complete heart-block. A contribution to the study of the action of strophanthus on the human heart. Arch. Int. Med., 1909, iv, 238.

(5) Bastedo: The signs of overdosage in digitalis administration. The Amer. Practitioner, 1912, xlvi, 609.

Digitized by Google

(6) BOEHM: Untersuchungen über die physiologische Wirkung der Digitalis und des Digitalein. Arch. ges. Physiol., 1872, v, 164.
(7) BORULTAU AND STADELMANN: Digitalis-behandlung und Herzarrhythmie. Deutsche Med. Woch., 1917, i, 43.
(8) BURRIDGE: Researches on the perfused heart. Some observations on the cardiac reserve. Quart. Jour. Med., 1915, ix, 43.
(9) BURRIDGE: Researches on the perfused heart. Some factors of the cardiac mechanism illustrated by reference to certain actions of barium and digitalis. Quart. Jour. Med., 1916, ix, 271.
(10) BOND: The effect of various agents on the blood flow through the coronary arteries and veins. Jour. Exp. Med., 1910, xii, 575.
(11) CAPPS AND MATTHEWS: Venous pressure and digitalis. Jour. Amer. Med. Assn., 1911, lvii, 151.
(12) CARO: Digitalis und Herzhypertrophie. Zeitsch. f. klin Med., 1910, lxx, 393.
(13) CHRISTIAN: Transient A-V dissociation with varying ventricular complexes caused by digitalis. Arch. Int. Med., 1915, xvi, 341.
(14) CHRISTIAN: The use of digitalis in the various forms of cardiac arrhythmia. Boston Med. and Surg. Jour., 1915, clxxiii, 306.
(15) CHRISTIAN: Chronic myocarditis. A clinical study. Jour. Amer. Med. Assn., 1918, lxx, 1909.
(16) CHRISTIAN: Digitalis therapy. Satisfactory effects in cardiac cases with regular pulse-rate. Amer. Jour. Med. Sc., 1919, clvii, 593.
(17) CLOETTA: Ueber Digalen (Digitoxinum Solubile). Munch. Med. Woch., 1904, li, 1466.
(18) CLOETTA: Ueber den Einfluss der Chronischen Digitalisbehandlung auf das normale und pathologische Herz. Arch. f. exp. Path. u. Pharm., 1908, lix, 209.
(19) CLOETTA: Ueber die Anwendungsweise der Digitalis Präparate. Correspondenz-Blatt f. Schweizer Aertze, 1919, xlix, 1193.
(20) COHN: Clinical and electrocardiographic studies on the action of digitalis. Jour. Amer. Med. Assn., 1915, lxv, 1527.
(21) COHN: The clinical pharmacology of digitalis. Med. Clin. of North Amer., 1917, i, 563.
(22) COHN AND FRASER: Certain effects of digitalis on the heart. Proc. 13th International Congress of Medicine, London, 1913.
(23) COHN, FRASER AND JAMIESON: The influence of digitalis on the T wave of the human electrocardiogram. Jour. Exp. Med., 1915, xxi, 593.
(24) COHN AND JAMIESON: The action of digitalis in pneumonia. Jour. Exp. Med., 1917, xxv, 65.
(25) COHN AND LEVY: A comparison of the action in Patients of g-Strophanthin and digitalis. Proc. Soc. Exp. Biol. and Med., 1920, xvii, 81.
(26) COHN AND LEVY: The effect of therapeutic doses of digitalis on the contraction of heart muscle. Proc. Soc. Exp. Biol. and Med., 1920, xvii, 160.
(27) CORRIGAN: Insufficiency of the aortic valve. Edinburgh Med. and Surg. Jour., 1832, xxxvii, 225.
(28) CUSHNY: On the action of substances of the digitalis series on the circulation in mammals. Jour. Exp. Med., 1897, ii, 233.
(29) CUSHNY: The therapeutics of digitalis and its allies. Amer. Jour. Med. Sc., 1911, cxli, 469.

Digitized by Google

(30) CUSHNY: Digitalistherapie. Berliner klin. Wock., 1913, l, 717.
(31) CUSHNY: Digitalis in auricular fibrillation. Jour. Pharm. and Exp. Ther., 1918, xi, 103.
(32) CUSHNY, MARRIS AND SILVERBURG: The action of digitalis in therapeutics. Heart, 1912, iv, 33.
(33) DANIELOPOLU: Arythmie complète chez l'homme provoque par la digitale: role du Systeme Moderateur. Comp. rend. Soc. de Biol., 1916, lxxix, 97.
(34) DANIELOPOLU. Action de la Digitale sur la Tension arterielle chez les Hypertendus. Arch. d. Mal du Coeur, 1917, x, 25.
(34a) DANIELOPOLU. Le traitment a la strophanthine par la methode des doses fractionnées, Presse med., 1921, xxix, 762.
(35) ECKLER: Experiments with the cat method for testing digitalis and its allies. The Lilly Scientific Bull., 1912, i, 55.
(36) EDENS: Ueber Digitalisbehandlung. Med. Klinik., 1907, iii, 1551.
(37) EDENS: Ueber Digitaliswirkung. Deutsch. Arch. f. klin. Med., 1911, civ, 512.
(38) EDENS AND HUBER: Ueber Digitalisbigeminie. Deutsch Arch. f. klin Med., 1916, cxviii, 476.
(39) EGGLESTON: Clinical observations on the duration of digitalis action. Jour. Amer. Med. Assn., 1912, lix, 1352.
(40) EGGLESTON: Clinical observations on the emetic action of digitalis. Jour. Amer. Med. Assn., 1913, lx, 757.
(41) EGGLESTON: Biological standardization of the digitalis bodies by the cat method of Hatcher. Amer. Jour. Pharmacy, 1913, lxxx, 99.
(42) EGGLESTON: Digitalis dosage. Arch. Int. Med. 1915, xvi, 1.
(43) EGGLESTON. The influence of large doses of digitalis and digitoxin on the blood-pressure in man. Jour. Amer. Med. Assn., 1917, lxix, 951.
(44) EGGLESTON: The treatment of advance heart failure. The Med. Clinics of North Amer., 1920, iv, 121.
(45) EGGLESTON. Administration of digitalis by "Eggleston method." Jour. Amer. Med. Assn., 1920, lxxiv, 733.
(46) EGGLESTON: The absorption of a digitalis body. Jour. Amer. Med. Assn., 1920, lxx, 463.
(47) EGGLESTON. Some newer concepts in digitalis therapy. Amer. Jour. Med. Sc., 1920, clx, 625.
(48) EGGLESTON AND HATCHER: The emetic action of the digitalis bodies. Jour. Amer. Med. Assn., 1913, lx, 499.
(49) EICHHORST. Die Behandlung Chronischer Herzmuskelinsufficienz. Deutsch. Arch. f. klin. Med., 1916, cxviii, 337.
(50) ETIENNE. Étude comparative de l'action physiologique de divers Dérivés et Preparations de la Digitale. Arch. Internat. de Pharm. et de Ther., 1909, xix, 119.
(51) FAHRENKAMP: Ueber die verschiedene Beeinflussung der Gefassgebiete durch Digitoxin. Arch. exp. Path. u. Pharm., 1911, lxv, 367.
(52) FAHRENKAMP: Elektrokardiographische Untersuchungen über die Einwirkungen der Digitalis bei der Arhythmia perpetua. Zentralbl. f. Herzkrank., 1914, vi, 219.
(53) FOCKE: Die Weiterentwicklung der physiologischen Digitalisprüfung. Zeitsch f. exp. Path. u. Ther., 1913, xiv, 262.

Digitized by Google

(54) FRAENKEL AND SCHWARTZ: Ueber intravenöse Strophanthininjektionen bei Herzkranken. Arch. exp. Path. u. Pharm., 1907, lvii, 79.
(55) FRASER: Strophanthus. Trans. Royal Soc. Edinburgh, 1890, xxxv, 955.
(56) FULTON: The use of digitalis. Providence Med. Jour., 1914, xv, 28.
(57) GARREY: The nature of fibrillary contraction of the heart: Its relation to tissue Mass and Form. Amer. Jour. Physiol., 1914, xxxiii, 397.
(58) GELBART: Über den Einfluss der Digitalis auf frisch entstandene Klappenfehler. Arch. f. exp. Path. u. Ther., 1911, lxiv, 167.
(59) GOTTLIEB. MEYER AND GOTTLIEB: Pharmacology, clinical and experimental. Trans. by Halsey, Phila. and London, 1914.
(60) GREENE AND PEELER: The central action of digitalis as tested by the cardio-inhibitory centre. Jour. Pharm. and Exp. Ther., 1915, vii, 591.
(61) HALE: Digitalis standardization and the variability of crude and of medicinal preparations. Hyg. Lab. Bull. no. 74, 1911.
(62) HALSEY, J. T.: The dosage and clinical value of different digitalis drugs and preparations. Southern Med. Jour., 1916, ix, 579, 677.
(63) HALSEY, J. T.: The digitalized dog's heart as affected by amyl nitrite and atropine, studied electro-cardiographically. Jour. Exp. Med., xxv, 729.
(64) HALSEY, R. H.: Profound effects of digitalis on the vagus producing severe detrimental subjective symptoms as shown by simultaneous electro-cardiograms and pneumograms. Proc. Soc. Exp. Biol. and Med., 1919, xvii, 36.
(65) HAMILTON: Pharmacological assaying. Jour. Amer. Pharm. Assn., 1919, viii, 49.
(66) HASKELL, MCCANTS AND GARDNER: The rate of absorption of various digitalis preparations from the gastro-intestinal tract. Arch. Int. Med., 1916, xviii, 235.
(67) HATCHER: The effects on the heart of "soluble digitoxin, Cloetta." Jour. Amer. Med. Assn., 1912, lviii, 921.
(68) HATCHER: The persistence of action of the digitalins. Arch. Int. Med., 1912, x, 268.
(69) HATCHER: The elimination of digitalis bodies. Jour. Amer. Med. Assn., 1913, lxi, 386.
(70) HATCHER: Digitalis therapy and the present shortage of drugs. Jour. Amer. Med. Assn., 1917, lxix, 1524.
(71) HATCHER: Some observations on the pharmacology of a digitalis body. Jour. Amer. Med. Assn., 1920, lxxv, 460.
(72) HATCHER AND BAILEY: Tincture of strophanthus and strophanthin. Jour. Amer. Med. Assn., 1909, lii, 5.
(73) HATCHER AND BAILEY: The clinical use of strophanthus. Jour. Amer. Med. Assn., 1910, lv, 1697.
(74) HATCHER AND BRODY: Biological standardization of drugs. Amer. Jour. Pharmacy, 1910, lxxxii, 360.
(75) HATCHER AND EGGLESTON: The emetic action of the digitalis bodies. Jour. Pharm. and Exp. Ther., 1912, iv, 113.
(76) HATCHER AND EGGLESTON: Observations on the keeping properties of digitalis and some of its preparations. Amer. Jour. Pharmacy, 1913, lxxxv, 203.
(77) HATCHER AND EGGLESTON: The stability of the infusion of digitalis. Jour. Amer. Med. Assn., 1915, lxv, 1902.
(78) HATCHER AND EGGLESTON: Studies in elimination of certain digitalis bodies from the animal organism. Jour. Pharm. and Exp. Ther., 1919, xii, 405.

Digitized by Google

(78a) HATCHER AND WEISS: Further observations on the seat of the emetic action of the digitalis bodies. Proc. Soc. for Exp. Biol. and Med., 1921, xix, 7.

(79) HEWLETT AND BARRINGER: The effect of digitalis on the ventricular rate in man. Arch. Int. Med., 1910, v, 93.

(80) HIRSCHFELDER: Effect of digitalis in experimental auricular fibrillation. Jour. Pharm. and Exp. Ther., 1915, vi, 597.

(81) HIRSCHFELDER, BICEK, KUCERA, HANSON: The effect of high temperature on the action and toxicity of digitalis. Jour. Pharm. and Exp. Ther., 1920, xv, 427.

(82) JAGIC: Ein Beitrag zur Kasuistik der Adams-Stokes'schen Symptom-Komplex. Zeitsch. f. klin. Med., 1908, lxvi, 183.

(83) JAMIESON: The action of the lethal dose of strophanthin in normal animals and in animals infected with pneumonia. Jour. Exp. Med., 1915, xxii, 629.

(84) JARISCH: Ueber Diuresehemnung durch Digitalis. Berlin klin. Woch., 1919, lvi, 1235.

(85) JONESCU AND LOEWI: Ueber eine spezifische Nierenwirkung der Digitaliskörper. Arch. f. exp. Path. u. Pharm., 1908, lix, 71.

(86) JOSEPH: Untersuchungen über die Herz-und Gefässwirkungen kleiner Digitalisgaben bei intravenöser Injection. Arch. f. exp. Path. u. Pharm., 1913, lxxiii, 81.

(87) KASZTAN: Beiträge zur Kenntniss der Gefässwirkung des Strophanthin. Arch. f. exp. Path. u. Pharm., 1910, lxiii, 405.

(88) KAY: The rapid administering of digitalis in cardiac decompensation. Cal. State Jour. of Med., 1919, xvii, 329.

(89) KOCKMANN: Beitrag zur Wirkung einiger körper der Digitalis Gruppe auf den N. Vagus. Arch. Internat. de Pharm. et de Ther., 1906, xvi, 221.

(90) KREHL: Zur Kenntniss des Digitalisgebrauchs und des Wasserwechsels. Deutsch. Arch. f. klin. Med., 1919, cxxviii, 165.

(91) LAWRENCE: The effect of digitalis on blood-pressure and pulse-pressure in the presence of cardiac decompensation. Boston Med. and Surg. Jour., 1914, clxx, 37.

(92) LEVINE: The action of strophanthin on the living cat's heart. Jour. Exp. Med., 1919, xxix, 485.

(93) LEVINE: The potency of some French digitalis preparations. Boston Med. and Surg. Jour., 1920, clxxxii, 64.

(94) LEVINE AND CUNNINGHAM: The margin of safety of intravenous digitalis in cats. Arch. Int. Med., 1920, xxvi, 293.

(95) LEVY AND CULLEN: Deterioration of crystalline strophanthin in aqueous solution. Its relation to hydrogen ion concentration and a method for its prevention. Jour. Exp. Med., 1920, xxxi, 267.

(96) LEWIS: Observations upon disorders of the heart's action. Heart, 1911–1912, iii, 276.

(97) LEWIS: Observations upon a curious and not uncommon form of extreme acceleration of the auricle, "auricular flutter." Heart, 1912, iv, 171.

(98) LEWIS: Evidences of auricular fibrillation treated historically. Brit. Med. Jour., 1912, i, 57.

(99) LEWIS: On cardinal principles in cardiological practice. Brit. Med. Jour., 1919, ii, 621.

(100) LEWIS: Clinical disorders of the heart beat. London and New York, 1918.

Digitized by Google

(101) Lewis: The mechanism and graphic registration of the heart beat. London and New York, 1920.
(102) Lewis, Feil and Stroud: Observations upon flutter and fibrillation. Part II. The nature of auricular flutter. Heart, 1920, vii, 191.
(103) Loewe: Neue Beobachtungen über Herz-funktion und Digitaliswirkung. Deutsch. Med. Woch., 1919, xlv, 1433.
(104) Loewi: Ueber den Zusammenhang von Digitalis und Kalziumwirkung. Münch. Med. Woch., 1917, lxiv, 1003.
(105) Macht and Colson: The toxicity of digitalis for normal and vagotomized cats. Jour. Pharm. and Exp. Ther., 1917, ix, 343.
(106) Mackenzie: New methods of studying affections of the heart. II. Action of digitalis on the human heart. Brit. Med. Jour., 1905, i, 587.
(107) Mackenzie: New methods of studying affections of the heart. III. Action of digitalis on the human heart. The effect on stimulus production and excitability. Brit. Med. Jour., 1905, i, 702.
(108) Mackenzie: New method of studying affections of the heart. IV. Action of digitalis on the human heart in cases when the inception of the rhythm of the heart is due to the ventricles. Brit. Med. Jour. 1905, i, 759.
(109) Mackenzie: Digitalis. Heart, 1911–1912, ii, 273.
(110) Martinet: Digitale et Faisceau de His. Presse Médical, 1911, xix, 563.
(110a) Marvin and White: Clinical studies of drugs of the "digitalis series." III. Apocynum and convallaria. Jour. Amer. Med. Assn., 1921, lxxvii, 1865.
(111) McCulloch: On the administration of digitalis to patients with diphtheria. Southern Med. Jour., 1920, xiv, 110.
(112) McCulloch and Rupe: Studies on digitalis dosage in children. Amer. Jour. Med. Sc. 1921, clxii, 231.
(112a) McCulloch and Rupe: On the tolerance of children for digitalis. Presented before the pediatric section of the Southern Medical Association. Nov., 1921.
(113) Meyer: Die Digitalis-Therapie: Ihre Indikationen und Kontroindikationen. Jena, 1912.
(114) Morris: Standardization of digitalis and the potency of the Minnesota leaf. Jour. Lancet, 1917, xxxvi, 176.
(115) Newcomb and Rogers: The effect of temperature on different samples of tincture of digitalis. Trans. Section on Pharm. and Ther., Amer. Med. Assn., 1918, 155.
(116) Ogawa: Ueber der Resorption wirksamer Bestandteile aus Digitalisblättern und Digitalis präparaten. Deutsch. Arch. f. klin. Med., 1912, cviii, 554.
(117) Pardee: The principles of the new methods of administering digitalis. New York Med. Jour. 1919, cx, 1064.
(118) Pardee: Notes on digitalis medication. 1. The rate of disappearance of digitalis from the body. 2. The therapeutic dose of tincture of digitalis. Jour. Amer. Med. Assn., 1919, lxxiii, 1822.
(118a) Pardee: Rate of absorption of digitalis from gastro-intestinal tract. Jour. Amer. Med. Assn., 1920, lxxv, 1258.
(119) Parkinson: Digitalis in soldiers with cardiac symptoms and a frequent pulse. Heart, 1917, vi, 321.
(120) Pongs: Ueber die zentrale Wirkung der Digitalis. Deutsch. Arch. f. klin. Med., 1917, cxxiii, 231.
(121) Pratt: On the importance of determining the potency of digitalis preparations. Boston Med. and Surg. Jour., 1910, clxiii, 279.

Digitized by Google

(122) PRATT: Digitalis therapy. Jour. Amer. Med. Assn., 1918, lxxi, 618.
(123) PRATT AND MORRISON: The activity of American digitalis. Jour. Amer. Med. Assn., 1919, lxxiii, 1606.
(123a) RAHN: Über Todesfälle nach Strophanthineinspritzungen und ihre klinische Bedeutung. Deutsches Arch. f. klin. Med., 1920, cxxxiii, 74.
(124) REINIKE: Nierenhypertrophie nach Digitalis. Zeitsch. f. klin. Med., 1914, lxxix, 296.
(125) REINIKE: Digitalis und Muskulatur. Zeitsch. f. klin. Med., 1914, lxxix, 441.
(126) ROBINSON: Paroxysmal auricular fibrillation. Arch. Int. Med., 1914, xiii, 298.
(127) ROBINSON: The influence of the vagus nerves upon conduction between auricles and ventricles in the dog during auricular fibrillation Jour. Exp. Med., 1916, xxiv, 605.
(128) ROBINSON: Auricular fibrillation: Its cause and its relation to ventricular activity. Internat. Clinics Series, 26, 1916, ii, 43.
(129) ROBINSON: The rapidity and persistence of the action of digitalis on hearts showing auricular fibrillation. Amer. Jour. Med. Sc., 1920, clix, 121.
(130) ROBINSON: The value of large single doses of digitalis in the treatment of heart disease. Southern Med. Jour. 1920, xiii, 396.
(131) ROBINSON AND BREDECK: Ventricular fibrillation in man with cardiac recovery. Arch. Int. Med., 1917, xv, 725.
(132) ROBINSON AND DRAPER: Studies on the action of the vagus nerve in man. I. The effect of vagus pressure in auricular fibrillation. Jour. Exp. Med., 1911, xiv, 217.
(133) ROBINSON AND HERRMANN: Paroxysmal tachycardia of ventricular origin and its relation to coronary occlusion. Heart, 1921, viii, 59.
(134) ROBINSON AND WILSON: A quantitative study of the effect of digitalis on the heart of the cat. Jour. Pharm. and Exp. Ther., 1918, x, 491.
(135) ROTH: The activity of wild American digitalis. Public Health Rep., 1917, xxxii, 377.
(136) ROTH: Digitalis standardization. The physiological evaluation of fat-free digitalis and commercial digitalin. Bull. Hyg. Lab., no. 102, 1916.
(137) ROWNTREE AND MACHT: The standardization of digitalis and the potency of American-grown digitalis. Jour. Amer. Med. Assn., 1916, lxvi, 870.
(138) SCHMIEDEBERG: Untersuchung über die pharmakologische wirksamen Bestandtheile der Digitalis purpurea. Arch. f. exp. Path. u. Pharm., 1874, iii, 16.
(139) SCHMIEDEBERG: Beiträge zur Kenntniss der pharmakologische Gruppe des Digitalis. Arch. f. exp. Path. u. Pharm., 1883, xvi, 149.
(140) SCHMIEDEBERG: Grundniss des Pharmakologie in bezug auf Arzneimittelehre und Toxikologie. 7th Auflage Leipzig, 1913.
(141) SCHMOLL: The tonic use of digitalis. Amer. Jour. Med. Sc., 1911, cxli, 35.
(142) SOLLMAN: Some conditions affecting the toxic dose of ouabain (strophanthin). Cleveland Med. Jour., 1915, xiv, 483.
(143) SOLLMANN: A manual of pharmacology and its applications to therapeutics and toxicology. Phila. and London, 1917.
(144) STEVENS: Some electro-cardiographic studies of patients under digitalis treatment. Boston Med. and Surg. Jour., 1916, clxxiv, 345.
(145) STEWART AND SCOTT: Studies on the circulation in man. XIV. Changes produced in the blood flow (in hands) under the influence of digitalis in cases of auricular fibrillation. Jour. Pharm. and Exp. Ther., 1915, vii, 263.

Digitized by Google

(146) Stone, Phillips and Bliss: A clinical study of pneumonia based on eight hundred and seventy-one cases. Arch. Int. Med., 1918, xxii, 409.
(147) Sutherland: The therapeutic action of digitalis on the rapid, regular rheumatic heart. Quart. Jour. Med., 1919, xii, 183.
(148) Von Tabora: Ueber die experimentelle Erzeugung von Kammer-systolenausfall und Dissoziation durch Digitalis. Zeitsch. f. exp. Path. u. Ther., 1906, iii, 499.
(149) Taussig: Complete and permanent heart-block following the use of digitalis in auricular fibrillation. Arch. Int. Med., 1912, x, 335.
(150) Turnbull: Paroxysmal tachycardia accompanied by the ventricular form of venous pulse. Heart, 1911–1912, iii, 89.
(150a) Voegtlin and Macht: The action of nitrites and drugs of the digitalis group on the isolated coronary artery. Jour. Pharm. and Exp. Ther., 1913, v, 77.
(151) Walters and Haskell: Susceptibility of the guinea pig to poisoning by digitalis. The Lilly Scientific Bull., 1912, i, 12.
(152) Wedd: Observations on the clinical pharmacology of digitalis. Johns Hopkins Hosp. Bull., 1919, xxx, 131.
(153) Weil: Beiträge zur klinische Electrokardiographie. Deutsch. Arch. f. klin. Med., 1914, cxvi, 486.
(154) Weil: Beiträge zur klinischen Electrokardiographie. II. Ergebnisse der Vagus-durchversuches. Deutsch. Arch. f. klin. Med., 1916, cxix, 39.
(154a) Weiss and Hatcher: Tincture of digitalis and the infusion in therapeutics. Jour. Amer. Med. Assn., 1921, lxxvi, 508.
(155) Wenckebach: The effects of digitalis on the human heart. Brit. Med. Jour., 1910, ii, 1600.
(156) West and Pratt: Clinical experience with a standardized dried aqueous extract of digitalis. Jour. Amer. Med. Assn., 1920, lxxv, 77.
(157) White: Auricular standstill: An unusual effect of digitalis on the heart, with especial reference to the electrocardiogram. Boston Med. and Surg. Jour., 1916, clxxv, 233.
(158) White, Balboni and Viko: Clinical observations on the digitalis-like action of squill. Jour. Amer. Med. Assn., 1920, lxxv, 971.
(159) White and Morris: The Eggleston method of administering digitalis with some notes on digitalis lutea. Arch. Int. Med., 1918, xxi, 740.
(160) White and Sattler: The effect of digitalis on the normal human electrocardiogram with special reference to A-V conduction. Jour. Exp. Med., 1916, xxiii, 613.
(161) Windle: Heart-block from drugs of the digitalis group. The comparative effects of digitalis, strophanthus, squill and apocynum. Heart, 1911–1912, iii, 1.
(162) Windle: Clinical observations on the effects of digitalis in heart disease with the pulsus alternans. Quart. Jour. Med., 1917, x, 274.
(163) Withering: An account of foxglove and some of its medical uses, with practical remarks on dropsy and other diseases. Birmingham, 1785.

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THE TREATMENT OF MENINGOCOCCUS MENINGITIS

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HISTORICAL RÉSUMÉ OF MENINGOCOCCUS MENINGITIS

First appearance

In the early part of the nineteenth century there appeared a form of epidemic disease which had not been observed before or at least it had not been recognized by the physicians of that time. According to Hirsch, it is not clear from the reports in the literature whether the disease previously had really existed. There is no reason to doubt that it had, but if so, it had been confused with many of the other forms of epidemic disease. This new entity was characterized by an inflammation chiefly or entirely localized in the cerebral and spinal meninges and it was accompanied by the symptoms of an acute epidemic constitutional malady.

The disease was first accurately described by Vieusseux, who observed a small epidemic at Geneva in 1805. Small outbreaks followed among the soldiers in the garrisons at Paris (1814), at Metz and Geneva (1815) and at Westphalia (1822). In the United States, cases were reported as far west as Kentucky and Ohio in 1808, and there was a widespread epidemic most prevalent in New England from 1814 to 1816.

The disease was first spoken of as "meningitis cerebrospinalis epidemica" or "typhus cerebralis." In this country it was known as "sinking typhus" or "spotted fever." From the date of its first appearance, meningococcus meningitis, epidemic meningitis or cerebrospinal fever has been epidemic in various places from time to time. These epidemics are followed by quiescent periods in which isolated cases appear and these quiescent periods are in turn followed after greater or less intervals of time by fresh outbreaks. This onward march has continued throughout the last century and up to the present day, so that either in sporadic or epidemic form meningo-

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coccus meningitis may justly be spoken of as an endemic disease. When once implanted in a new community, it there remains just as is the case with measles, scarlet fever and other similar diseases so that at present it still prevails in those countries in which it first appeared a century ago.

For many years meningococcus meningitis was regarded as a disease which followed none of the laws which govern the progress of other epidemic diseases. An epidemic would begin as a perfectly isolated incident in a locality that had been altogether free before, run its course there, and then spring up in some quite distant region. The cause of such transmission by means of "carriers" was of course not then known. While the disease is most commonly seen in children, with bad sanitary and overcrowded housing conditions it quickly develops epidemic proportions and affects people of all classes and of all ages. The statistics compiled by Compton show that the most susceptible age for the sporadic form is under five years and the least susceptible from thirty-five to forty years; during epidemics persons of all ages are attacked. Even in epidemics and in the outbreaks occurring in army barracks during the world war, the disease has a seasonal prevalence. The majority of the epidemics have begun in the winter months, the maximum intensity of the epidemic being reached during the spring months and from then on the incidence of disease falls steadily and the epidemic is usually over by the early summer months. Our present conception of meningococcus meningitis is that of an infectious disease, occurring sporadically or in epidemics, due to the diplococcus intracellularis meningitidis, discovered by Weichselbaum. The disease affects children and young adults most frequently, the latter especially when closely confined in army barracks and institutions. It prevails chiefly in the winter and spring months. The mode of infection is by direct contact either with a patient suffering from the disease or contact with a healthy person harboring the organism, a so-called carrier.

Mortality before serum treatment

From a review of the literature it is apparent that the severity of the disease unmodified by treatment has not changed materially since its first recognition. In the earlier epidemics the mortality is

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given from 20 to 75 per cent by Hirsch, who collected the statistics from 41 epidemics. The figures before the days of serum treatment, compiled by Flexner, show that the death rate in 18 epidemics was between 42.5 and 90 per cent. In one epidemic the mortality was 42.5 per cent; in three, 60 per cent; in nine, 70 per cent; in two, 80 per cent, and in one, 90 per cent. Statistics show, moreover, that the mortality varies considerably with different epidemics and at different periods of the same epidemic. Fulminating and rapidly fatal cases are by far more frequent at the beginning of epidemics and mild and abortive cases much more frequent toward the close. Sporadic cases are usually mild and the mortality with this form of disease is relatively low.

Treatment before discovery of antimeningococcus serum

As with other diseases whose etiology and pathology have not been clearly understood and in which the views regarding the nature of the disease have changed from time to time, so with meningococcus meningitis the methods of treatment have been ever changing and many diametrically opposed therapeutic measures have been adopted from time to time. Among the most prominent and characteristically different methods have been: a stimulating and tonic method pursued because the disease was one of "utter prostration;" vigorous antiphlogistic measures such as the use of mercury in large quantities or of repeated bleeding, and sedative measures such as the use of large doses of opium.

Emetics were held to be useful if not indispensable in the early stage of the disease and Vieusseux in the first epidemic said "The first principle and often the only remedy was tartar emetic." A half grain was given every ten minutes to produce full and free vomiting and the dose was repeated five or six times or more often according to its effect. "Sometimes it arrested the vomiting, the fever and the pain in the head immediately, and was generally sufficient for the cure." Some writers were less sanguine as to the beneficial effects of emetics and a few indeed condemned their use. Nearly all writers advised them during the early period of the disease with the idea in mind "to scatter the congestion which produced the exudative inflammation of the cerebrospinal membrane, and to aid in eliminating the morbid material of the disease."

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In the early epidemics, with the exception of mercury which was not then regarded as a purgative, it was the general consensus of opinion that there was no room for cathartics in this disease. They were even regarded as harmful to the patient. One writer says "The constipation, if any exists, yields usually without purgative medicine; constipation is in fact and as far as it goes a sign of health rather than of disease."

In such an extremely fatal disease and one in which but little hope was held of its arrest by natural means, active measures were used frequently and boldly. Venesection was employed by all. Large quantities of blood were taken from the arm or jugular vein at one time or several bleedings were made in quick succession. As much as 48 and 44½ ounces of blood have been removed from an adult on separate occasions. In a child, 48 ounces of blood were taken by cups from the neck and occiput and 26 ounces from a vein in the arm within eighteen hours. Local blood-letting did seem to be followed by some good results, especially in the sthenic cases. The effects were not regarded as satisfactory although in many cases there was noted an improvement in the pulse rate and relief from the excruciating pain in the head. But the general impression prevailed that while blood-letting afforded considerable relief to the patient in the early stages, it was a disappointment from a curative point of view.

Cold to the head and spine, leaches to the head, blisters and dry and wet cupping were used for the relief of the severe pain and afforded some relief and comfort to the sufferers. Great stress was laid upon the necessity for maintaining the bodily heat and for keeping the skin moist. Warm and hot baths, bottles of hot water, billets of wood heated in boiling water and wrapped in flannels, hot infusions, etc., were considered of great help in combating the violent symptoms as well as the symptoms of collapse.

Alcohol, opium, iodide of potassium and other drugs were used generously and their usefulness and indications were the subject of much discussion. There were many who believed that alcoholic stimulants were absolutely necessary "to support the vital energy, to raise the patient from his depressed state and to hold him up until the disease passes off." Other writers, especially the European writers, were more skeptical of the use of stimulants and condemned

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their liberal and indiscriminate administration. Opium enjoyed the reputation of being a specific for meningococcus meningitis. It was given by some in small doses and by others in large doses; although its curative effects were grossly overestimated, it was observed that "the pain and spasm subsided, the skin became warmer, the pulse fuller and the entire condition of the patient became more hopeful" after its administration. Iodide of potassium was extensively employed to promote absorption during the late stage of the disease.

Among the active measures advised in the treatment in the early epidemics, mercury perhaps was used more generally than any other medicine. Mercury was given by mouth or inunction even to the point of salivation, but as with the other measures adopted, we find a diversity of opinion regarding its beneficial effects. Other measures such as the proper use of a nutritious diet and of tonic medicines received their share of attention.

Stillé concisely stated the opinions regarding the peculiarities of the disease and its treatment which were held during the early history of the disease. He said:

> In epidemic meningitis as in other acute and especially epidemic diseases, many cases are fatal from the outset; the first symptoms of the attack are the first phenomena of death; on the other hand many are so slight as scarcely to require medicinal interference for their cure. But the event of many others is determined by the appropriateness and the opportuneness of the treatment . . . . but their successful application depends upon the sagacity of the physician.

The use of the more modern measures, repeated lumbar puncture, the intraspinous injection of antiseptics, permanent drainage, etc., in the treatment of meningococcus meningitis will be discussed later.

THE MENINGOCOCCUS AND ITS STRAINS

The micrococcus intracellularis meningitidis was first accurately described by Weichselbaum in 1887 as a Gram-negative coccus, usually occurring in pairs. Prior to, as well as subsequent to his report, it had erroneously been stated that this organism was Gram-positive. The meningococcus, except for older laboratory strains

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which can thrive on plain agar, grows only on media enriched with blood, ascitic fluid or starch. The colonies are round, perfectly lenticular with smooth edges, are translucent by transmitted light and a bluish gray by reflected light. They are rarely over 2 mm. in diameter. The optimum temperature for growth is 37.5°C.; comparatively slight variations from this will retard the growth on culture media. The meningococcus is sensitive to drying and cultures rarely survive longer than seven days. Recently it has been demonstrated that reduced oxygen tension greatly facilitates cultivation of the meningococcus.

Like the gonococcus, the meningococcus ferments dextrose and maltose. For a time it was difficult to differentiate these two organisms except by noting their origin. They are, however, distinct as was rather drastically proven by injecting cultures of each into the urethra of two healthy men. The individual receiving the gonococcus developed gonorrhea while the one receiving the meningococcus had no reaction. These two organisms are frequently agglutinated by the same sera, but Ellis in 1915 demonstrated that the immediate agglutination reactions are specific, i.e., that even at dilutions of 1:2, meningococcus sera would only agglutinate the meningococcus immediately or within one-half hour while after an interval of an hour or so the gonococcus would also be agglutinated.

In 1909, Dopter isolated an organism from the spinal fluid of a patient with meningitis that had all of the morphological and cultural characteristics of the meningococcus but was not agglutinated by the usual meningococcus serum. This organism he called the parameningococcus. Wollstein not only corroborated Dopter's observation but found that there were a number of intermediate strains which although similar could be distinguished serologically from the normal and the parameningococcus. Later, still further variants were reported. Gordon immunized a series of rabbits with 34 cultures of meningococci collected during the early part of the war and carried out agglutination and absorption reactions with his strains. He found that they fell into four groups which he designated as I, II, III and IV. I and III, and II and IV were closely related, and their sera showed cross agglutination but they could be separated by absorption tests. Groups I and II were the more common. Ellis

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by more or less similar methods described three groups. Nicolle and his co-workers at the Pasteur Institute reported four divisions of meningococci, namely, A, B, C and D, of which B was identical with Dopter's parameningococcus. At the Rockefeller Institute two main groups of meningococci, the normal and paranormal and two or more intermediates are recognized. Many attempts have been made to classify the groups described by these various authors. In Davison's experience, the Pasteur A, Gordon's I and III and the Rockefeller Institute paranormal are agglutinated by the same sera and the Pasteur B, Gordon's II and IV and the Rockefeller Institute normal by the same sera. These two main divisions of four groups each are those most frequently encountered. It is interesting that in England in 1914 and 1915 the members of the first group were the more common, not only in the army but also among the civilian population while during 1917 and 1918 the members of the second group were the more frequent, possibly indicating that an immunity had arisen against the members of the first group. The Pasteur C and D, Gordon's III and IV and the Rockefeller Institute intermediates are comparatively rare.

THE DISCOVERY OF A SPECIFIC SERUM

The discovery of the meningococcus and the gradual development of the routine employment of lumbar puncture resulted in a clearer understanding of meningococcus meningitis and made it possible to establish an accurate diagnosis, which before had been impossible. In spite of these important observations, no therapeutic measures were suggested which in any way influenced the heavy mortality until the discovery of antimeningococcus serum. The production of the specific serum is the direct result of the world wide epidemic which continued almost without cessation from 1904 to 1910. Almost simultaneously Jochmann in Germany and Flexner in New York studied the production of specific immune sera which would protect small animals against infection with meningococci. They could protect small animals and Flexner was able to cure meningitis, artificially produced in the monkey by the intraspinous injection of an immune serum which he prepared. Antimeningococcus serum for use in human beings was produced on a large scale by the immunization of the horse.

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In 1906, Jochmann reported the results with 11 cases of meningitis in human beings treated by the intraspinous injection of serum, and in 1907, Kolle and Wassermann who also had prepared an immune serum reported the results of treatment in 57 cases of meningococcus meningitis. In 1908, Flexner and Jobling published a comprehensive report of serum treated cases. There was an appreciable alteration in the death rate in all cases treated when the injection was made into the subarachnoid space. Park in 1905 had used an antimenigococcus serum which he had prepared in the treatment of 20 cases by subcutaneous injection. The results were not satisfactory. The serum was at first injected subcutaneously and intravenously as well as intraspinously, but later the intraspinous method alone was employed by all. Thus, as the direct result of scientific research, a satisfactory specific serum therapy was finally developed. For more than fifteen years antimeningococcus serum has now been used and its efficacy is universally admitted.

THE PREPARATION OF ANTIMENINGOCOCCUS SERUM

The production of antimeningococcus serum was first accomplished by Jochmann by injecting cultures of the meningococcus heated to 60°C. for one-half hour intravenously into horses. Increasing doses of killed organisms were injected at stated intervals and later the horses were injected with cultures of living meningococci. Kolle and Wassermann in addition to the killed and living organisms injected the autolysate as well, as they thought the soluble products of the meningococcus increased the potency of the serum. Flexner, who used at first increasing doses of killed organisms, then increasing amounts of autolysate and then living cultures by the combined subcutaneous and intravenous method, finally discarded the intravenous method as the injections were followed by such severe and alarming reactions and resorted to the subcutaneous injection of cultures and autolysate alternately at seven-day intervals. Subcutaneous inoculations were followed by a mild febrile reaction during which the animal ate less but did not suffer from other symptoms. The dose was gradually increased from 1 to 2 and 3, etc., loops of cultures to the amount contained in one and a half small culture bottles and the dose of autolysate was increased to the equivalent of one and

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one-half bottles of the cultures. Many different strains of meningococci were employed in the production of Flexner's serum. As new strains were found, they were added to those already in use in order to have antibodies in the serum which corresponded to all the recognized strains. Immunization in the horse is a slow process and sera withdrawn less than six months after the beginning of injections are apt to be deficient in antibodies. The antiserum first used by Flexner was obtained from a horse who had been in process of immunization over one year. After the discovery of the two main types of meningococci, the normal and parameningococcus, representatives of these two types were used in the preparation of sera either in mixtures or with alternate injections of the two types. It was learned that the employment of representative normal and representative parameningococcus strains was not sufficient for immunization as within each group there were organisms which reacted weakly to the specific antibodies produced by other strains of the same group. When the weakly reacting strains were inoculated, antibodies were formed to which they reacted strongly. So not only one but several strains of each group were employed for the purpose of immunization of the horses. It is of the utmost importance that serum used therapeutically contains the antibodies specific for the infecting strain.

Rapid method of preparing serum

As mentioned before, from six to twelve months were required to produce a meningococcus serum of high potency by the old method of immunization. The increase in the number of cases of meningococcus meningitis which was evident in the early days of the great war made it imperative that a larger amount of serum would be necessary than could be supplied by the ordinary methods of production. For this reason and because much of the sera prepared by the commercial houses had given such irregular and disappointing results, the preparation of serum in large quantities was undertaken at the Rockefeller Institute. Amoss and Wollstein have produced a polyvalent serum of high titre. By first desensitizing the horse before employing the full inoculation of the culture, according to the technique of Briot and Dopter, the severe reactions usually occur-

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ring after intravenous injection were avoided. Three successive cultures of representative strains of meningococci and their autolysate were injected intravenously at regular intervals. Specific immune bodies appear early in this serum and increase rapidly. A potent serum was produced in eight or twelve weeks instead of the eight or twelve months which the older method required. This serum has been successfully employed in the treatment of meningococcus meningitis.

Many sera of high potency are prepared and can be obtained. The most satisfactory, however, have been those prepared by research laboratories: the Rockefeller Institute in this country and the Pasteur Institute in France. The Lister Institute now prepares a polyvalent serum in which the horses are immunized by the four representative strains of meningococci differentiated by Gordon. The experience of the British forces with commercially prepared antimeningococcus sera should not be forgotten for it emphasizes the necessity for the standardization of sera prepared by commercial laboratories. Sera should not only contain antibodies for the four representative strains of meningococci and be of high titre but they should not be colored by hemoglobin compounds and a harmless chemical preservative should be used. Tricresol not only will prevent contamination of serum which has been collected and bottled in a sterile manner but it has an analgesic effect also.

Standardization of serum

Different opinions are held regarding the methods for determining the therapeutic value of antimeningococcus serum, as it is much more difficult to determine the potency of an antibacterial serum than of an antitoxic serum, such, for instance, as diphtheria antitoxin. Krauss and Dörr believe that the chief action of the serum depends upon its antitoxic properties; Jochmann, Flexner and Wassermann believe that the chief action of antimeningococcus sera is to increase phagocytosis of the microörganism, to destroy the meningococcus and to neutralize toxins. It has been shown that antimeningococcus serum probably contains bacteriolysins, opsonins, antiendotoxins, agglutinins, precipitins and complement fixation bodies. The presence of many of these does not necessarily have any influence on

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the therapeutic activity of the serum. Different writers have suggested the use of various tests to fix a proper standard for antimeningococcus serum but the difficulty in using any one criterion as a standard for measuring the several forms of activity is apparent. The opsonin and the complement fixation methods have practically been discarded as it is not possible to determine by them the antibodies representing the different types of meningococci. The antiendotoxic standard as applied by Dopter, Wassermann, Krause, Leuchs and others has been criticized by Gordon on the ground that the content of endotoxin was too low to be used for purposes of standardization. Before this method becomes an acceptable method of standardizing meningococcus serum, the presence of a meningococcic endotoxin must definitely be proven. The workers in the Hygienic Laboratory in Washington have failed so far to confirm the presence of an anti-endotoxin in the sera which they have tested (Leak). The protective power of antimeningococcus serum for small animals has been used as a method of standardization. The test is made by mixing varying amounts of a meningococcus emulsion with a definite quantity of immune serum and injecting this mixture into the peritoneal cavity of animals. Hitchens and Robinson have described a protection test with mice and believe that the animal protection test is more nearly indicative of the potency of the serum than is the agglutination test or the complement fixation test. They also suggest that the amount of serum necessary to protect against one minimum lethal dose of culture be used as a uniform standard for antimeningococcus sera. Amoss and March were unable to confirm their results and regard the protective power of antimeningococcus serum for laboratory animals as a variable and unsuitable index of its value.

At the present time the determination of the agglutinin content of sera is considered, in this country, the most reliable method for the standardization of antimeningococcus sera. Although the part played by agglutinins in overcoming infection is not known, it has been demonstrated that a high agglutination titre is usually accompanied by a strong complement binding power and a high opsonic index. It is therefore reasonable to suppose that a serum possessing these properties has a relatively high antibody content. Practical experience has shown that sera showing a high agglutination titre for the

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meningococci isolated from patients' cerebrospinal fluid as a rule give good therapeutic results. On the other hand, as the French writers have pointed out, satisfactory clinical results may at times be secured by the use of sera with a low agglutination power. At present it must be admitted that the methods of determining the potency of antimeningitis sera leave much to be desired. The New York State Board of Health requires that serum should be prepared from four properly chosen cultures of meningococci and a standard value based on the agglutination titre. Serum used in treatment of this disease should contain antibodies for the two main types of organisms and the subtypes.

Serum for diagnostic purposes

Polyvalent and monovalent antimeningococcus sera are used, in the laboratory, for identifying the meningococcus, for determining the various types of meningococci and for testing the potency of different sera. The therapeutic polyvalent serum prepared in the horse is used for this purpose. Monovalent sera are made in young rabbits according to two methods. Amoss prepares his serum by suspending a sixteen-hour growth of the meningococcus in 10 cc. of 0.8 per cent salt solution. Of the suspension 0.1 cc. is diluted to 2 cc. and injected intravenously. The same dose with a fresh culture is repeated on the second day and one-eightieth of a culture on the third day. After five days, one-eightieth of a culture, then one-fiftieth and finally one-twenty-fifth on the third day are injected. Two days later the rabbit is sacrificed and the serum collected. Hines prepares his serum by injecting increasing doses of an emulsion of meningococci killed by heat. The serum is preserved with phenol. By either one of these methods satisfactory sera for identification of the type of meningococcus by the agglutination test are prepared. The reader is referred to text books for a description of these tests.

DIAGNOSIS OF MENINGOCOCCUS MENINGITIS

In the early stage of meningococcus infections before the localization of the organism in the meninges with the resulting symptoms of meningeal irritation, diagnosis is well nigh impossible except in the presence of an epidemic. Even with the aid of blood cultures diag-

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nosis before the onset of meningitis is most difficult. The symptoms at the onset may be so mild and so insidious that several days may elapse before the true nature of the infection is recognized, or it may be so severe and fulminating that the patient dies within the first twelve to thirty-six hours. A sudden onset with chills, marked prostration and headache, together with vomiting, is highly suggestive of meningococcus meningitis, especially when there is a petechial or purpuric rash. The characteristic but by no means pathognomonic eruption occurs at some time or other during the course of the disease in about 50 per cent of the cases. As it is not a constant finding, it cannot always be relied upon. Occasionally one sees patients within the first few hours of the onset without meningeal symptoms when petechiae are present but in the majority of cases meningococci will be found in the cerebrospinal fluid if it is examined even at such an early period. Although a tentative diagnosis of meningococcus meningitis may be made when a patient who previously has been well has an acute onset with headache, vomiting, a chill or convulsions and who presents the signs of meningeal irritation (cervical rigidity, hyperaesthesia, Kernig's sign, Macewen's sign or a tense and bulging fontanelle), the final diagnosis always rests on the actual demonstration of meningococci in the cerebrospinal fluid. A differentiation between meningitis due to the pneumococcus, streptococcus, staphylococcus aureus and other organisms and between other diseases, pneumonia, typhoid fever, typhus fever, cerebral abscess, simulating meningococcus meningitis, can be made in no other way than by lumbar puncture and the demonstration of the organism. A clinical diagnosis without bacteriological proof is always open to criticism. In the very early stages the cerebrospinal fluid may appear clear yet the meningococcus can often be demonstrated in both stained smears and cultures. As the disease progresses the cerebrospinal fluid becomes turbid and intracellular and extracellular Gram-negative diplococci can usually be made out readily. In almost all cases they will be found after prolonged search. In the subacute and chronic cases the demonstration of the meningococcus may be attended with great difficulty. I have seen patients in whom it was impossible to demonstrate the organism either by smear or by culture in the cerebrospinal fluid at the first puncture but in subsequent punctures

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they appeared in large numbers. In some patients, particularly children, when the disease has been present for some days, there may be an obstruction to free communication between the spinal subarachnoid space and the interior of the ventricles. In these circumstances it sometimes happens that no fluid can be obtained by lumbar puncture or the fluid that is obtained may be free from meningococci whereas the ventricular fluid contains the organisms in large number. Only by means of a ventricular puncture is it possible to obtain cerebrospinal fluid and so demonstrate meningococci. This may readily be accomplished in children with an open fontanelle which is the age at which the severance of the communication is more likely to occur. Relatively few cases are seen in which meningococci cannot be demonstrated by persistent search in the cerebrospinal fluid removed from the ventricle or lumbar subarachnoid space at different times. That such cases do occur and recover after specific therapy should be borne in mind. In a series of 202 cases of meningococcus meningitis which I have seen during the past few years, there were 13 cases in which meningococci were not demonstrated in smear or by cultivation. Corroborative evidence of the existence of meningococcus infection may be had by demonstrating the organism in the rhino-pharynx of such patients. The following case is cited as an example:

J. D., white, age seven years. Patient was admitted to the Harriet Lane Home on the 114th day of the disease, with a history of recurrent attacks of fever, headache, vomiting, drowsiness, muscular rigidity and opisthotonus. On admission, examination revealed nothing abnormal except emaciation, hyperactive reflexes and slight engorgement of the vessels of the fundi.

Temperature, 99.6°F, white blood cells, 16,700. Pirquet negative. Wassermann negative. Urine normal. Blood culture sterile. Throat culture showed meningococci.

Spinal fluid: No increase of pressure, slightly cloudy, 2800 white blood cells; 76 per cent polymorphonuclears. Pandy strongly positive, Wassermann negative. No organisms found in smears. Culture sterile.

Treatment: Six lumbar punctures were done and antimeningococcus serum injected three times. The spinal fluid gradually became clear, cell count fell to 32 per cubic millimeter. Pandy test remained positive. Repeated

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examinations failed to show organisms in smears and repeated cultures were sterile. The patient was apparently well 122 days after the onset of the disease.

PROPHYLACTIC MEASURES IN MENINGITIS

Epidemiological studies of meningococcus meningitis have established without doubt that the disease is spread by direct contact from one person to another, as is the case with diphtheria, poliomyelitis, etc. More than twenty years ago Councilman, Mallory and Wright, Kiefer and others demonstrated that the meningococcus is present in the rhino-pharynx of patients suffering from meningococcus meningitis. In 1901, Albrecht and Ghon demonstrated its presence in healthy persons. Since then it has been generally accepted that the disease is spread by means of the rhino-pharyngeal secretions that harbor the meningococci. Therefore, from the standpoint of the management of meningococcus meningitis, prophylaxis may be said to equal in importance specific serum treatment. As ill persons are usually confined to their beds, they are of menace only to physicians, to attendants and to other patients and do not become a menace to others until the convalescent stage.

Meningococcus carriers

The healthy carrier is the greater menace to the community. The disease is spread by those who have suffered from the disease, and by those who have never been ill. The meningococcus may remain in the rhino-pharynx of a carrier for a variable length of time and for that reason two classes of carriers can be distinguished, the acute or transient carrier and the prolonged or chronic carrier. Attendants and relatives constitute the larger percentage of the acute carriers, and usually the meningococcus remains in the rhino-pharynx for only a short period of time. It may be found at one examination and not at subsequent ones. The British Medical Research Committee found that of 119 people who had been in contact with meningitis patients, themselves not being ill, 94 harbored organisms of the same type as had caused disease in the patient with whom they had been in contact. The chronic carrier is different. He has usually suffered from the disease himself and the organism persists for months, even

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years, and while it occasionally disappears, it subsequently reappears. The spread of the meningococcus, an organism which does not withstand, easily, exposure to air, is accounted for by chronic carriers. These are in all probability responsible for the spread of the disease from place to place and for the causation of epidemics. If it were not for them the disease might readily die out. The cycle of events which leads to contamination and to infection has been summarized by Flexner as follows: "A meningococcus carrier is introduced into a group of persons of the more susceptible ages. Of the latter a certain number become contaminated through aspirating the rhino-pharyngeal secretions which he ejects. Of those thus contaminated a variable number actually become infected and develop meningitis while a larger number are converted either into temporary (evanescent) or more enduring (chronic) carriers. The patient during the acute illness and for an indefinite period while convalescent is also a carrier. Hence the number of carriers produced exceeds the number of cases of infection, from which it may be concluded that the individual susceptibility to epidemic meningitis is low." It has been shown by a number of workers (Mayer) that the percentage of healthy carriers both in the civil population and in garrisons is generally about 3 per cent. The constant occurrence of sporadic cases of meningococcus meningitis is thus readily explained. There must be subsidiary factors, however, to explain the occurrence of local and general epidemics. It is difficult to account for the sudden occurrence of a widespread epidemic of meningitis in a city in which meningitis has been endemic for years. An alteration of the type and virulence of the bacterium or the introduction of a new type of increased virulence suggest themselves as explanations but they are explanations without proof.

Hygienic measures

The regulation of the factors that produce local epidemics constitute the more important hygienic measures which should be observed in the management of patients with meningococcus meningitis. These factors are chiefly overcrowding and poor ventilation. Proper ventilation must be maintained at all costs and the prevention of overcrowding is imperative. By these measures especially in insti-

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tutions, in barracks and on ships the risk of the contamination of persons by contact with carriers is greatly lessened. The rise in the incidence of the disease during the cold and damp months of the year undoubtedly is to be explained by the tendency of individuals to congregate together in poorly ventilated and overheated rooms. In a British naval barrack during the month of October, there were 23 cases of cerebrospinal fever, the number of cases immediately fell to 6 for November and 2 for December with the order that the windows should be open day and night and the hammocks hung not closer than every 2½ feet (Rolleston). Free ventilation, isolation and a proper amount of space are as necessary for the treatment of patients with meningococcus meningitis as for the prevention of the disease. Attention should be given to the prevention of overfatigue and the control of rhino-pharyngeal infections—factors which have a tendency to favor the spread of the disease. The proper observing of these principles is of particular importance during time of war and in epidemic areas where there are large numbers of individuals crowded together in barracks improperly ventilated. It was shown by Mayer and his colleagues that there were 2.46 per cent carriers among 1911 soldiers in barracks during epidemic free times whilst the Medical Research Committee found 8.53 per cent among 1629 soldiers who had been in contact with 60 cases of meningococcus meningitis.

The prevention of infection of attendants in charge of patients with meningococcus meningitis is chiefly concerned with the discharges from the rhino-pharynx. It is advisable that patients be isolated either in separate cubicles or by the less expensive method of separating the beds by intervals of 2½ feet and hanging sheets between them. The attendants should not expose themselves to the breath of the patients; they should be protected by wearing caps, gowns and mouthpieces when caring for patients. Nurses should thoroughly cleanse their hands with soap and water and a disinfectant solution after each contact with patients and with all articles used by patients. The discharges from the nose and throat, the conjunctivae, and herpes, and excreta should be destroyed. All articles which come in contact with patients should be kept separate and thoroughly disinfected. Cerebrospinal fluid and the apparatus used in giving treatments should receive special care and sterilization. Cultures should

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be taken at stated intervals from those in attendance on patients to be sure that they have not become carriers. Convalescent patients should not be discharged from quarantine until it has been proved that meningococci are not present in the rhino-pharynx.

Prevention of the spread of meningococcus meningitis depends on the detection of carriers, their isolation and their treatment. The question of general examinations for the detection of carriers of the meningococcus has received much attenton especially during the epidemic which occurred among troops during the late war. Certain investigators (Flexner, Parkes, etc.) believe that the incidence of the disease was lower among the troops in which routine search for carriers had been carried out, whilst others, notably Galambos Klinger, Rouman, etc., believe that the incidence of the disease is not influenced by the detection and segregation of the healthy carriers. The bacteriological control of carriers with their detention and proper treatment is the only means of properly checking and preventing the spread of the disease. Indeed, the disease might be exterminated if it were possible to detect and isolate all the carriers of the meningococcus. The difficulties, however, are too great at the present time to carry out such drastic measures as this would entail. The search for carriers among contacts should, however, be carried out whenever meningococcus meningitis arises and the carriers should be isolated and proper treatment instituted. The carriers should be kept isolated until three successive negative cultures at five-day intervals have been obtained. A regulated period of quarantine is quite useless and effective control can only be had by bacteriological proof of negative cultures. The bacteriological detection of carriers necessitates careful technique in the making of the cultures and the cultivation of the meningococcus, the identification and differentiation from other Gram-negative cocci, which frequent the rhino-pharynx, agglutination tests and the recognition of the different types.[1]

The transient carrier usually becomes free from meningococci in a week or ten days and the number of colonies grown from the rhino-

[1]The reader is referred to the standard technique of meningococcus carrier detection adopted by the Medical Department of the United States Army and Navy and the United States Public Health Service for detailed information regarding the methods in use.

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pharynx is much fewer than is the case with the chronic carrier. Carriers should be separated from those who have become negative in order to prevent reinfection and carriers should be separated according to the type of organism to prevent cross infection. The chronic carrier is the greatest menace to the community and offers the greatest problem in treatment. As Flack has shown, the persistence of the carrier state varies within fairly wide limits. Among 185 carriers, 124 were known to have been in contact with a case of meningitis or another carrier, whereas 61 had not been in contact either with a patient or with a carrier. The average duration among the former was 4.65 and among the latter 3.68 weeks. Twenty per cent of the 185 carriers became free of organisms within the first two weeks, 52 per cent within the first four weeks and 5 per cent persisted beyond twelve weeks. It was noticed that sunshine and dry weather apparently influenced the rapidity with which the carriers became free. In February and March, the rate of discharge of carriers from isolation was slow whilst with the coming of sunshine and dry weather in April the rate of discharge was increased. Although in the great majority of carriers the rhino-pharynx is normal, the meningococcus persists for a longer time in those who are subject to inflammatory conditions of the rhino-pharynx and accessory sinuses.

Treatment of carriers

It is clear that the meningococcus disappears from the rhino-pharynx spontaneously in the overwhelming majority of carriers. Fresh, dry air and sunshine undoubtedly have an important and favorable influence on the rapidity with which the meningococci disappear. Chronic inflammatory conditions of the rhino-pharynx require appropriate treatment. Aside from these measures the efforts to hasten the disappearance of the meningococci in convalescent patients and carriers by antiseptics have been most discouraging. As the meningococcus is one of the least resistant of the pathogenic organisms to disinfectants, it seems surprising that a means of destroying it has not been found. The reason probably is not so much its resistance to the various antiseptics which have been employed as the difficulty in bringing the solution actually in contact with the organism in the

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rhino-pharynx and accessory sinuses. Strong antiseptics by injuring the mucous membrane and setting up inflammatory conditions actually prolong the carrier state (Fulloch). Many methods with mild antiseptics have received careful trial. Swabs, douches, sprays and vapors have been employed. Antiseptics which destroy the meningococcus in vitro fail to destroy the organisms when they are used in the human being. Colebrook and Tanner in tests made upon the meningococcus contained in a film of nasal secretion found that weak carbolic acid solutions and a 5 per cent suspension of "argentine" killed the meningococci. The substance was non-irritating to the mucous membrane and temporarily rendered the carrier free from meningococcus; the organism, however, reappeared in the majority of cases. Attempts with zinc sulphate and pyocyanase have also been unsuccessful. Kutscher after the recommendation by Kolle and Wassermann reported satisfactory results with the nasal sprays of dry antimeningococcus serum. Their results were not confirmed by other observers. Many different substances have been tried in the form of vapors and inhalants. Compounds of iodine, guaiacol, thymol and alcohol were tried by Vincent and Vellot. These likewise have not been followed by very satisfactory results. Sophian found that a 0.5 per cent hydrogen peroxide solution used as a nasal spray and gargle rendered the rhino-pharynx free from meningococci in the majority of cases within a few days to two weeks. Normal salt solution and potassium permanganate solution have likewise been tried, but as has been the case with the other methods which have been employed, although the organism tends to disappear, it usually reappears after a few days. Worster-Drought and Kennedy used extensively a solution of chloramine T of 2 per cent strength diluted with warm water just before use. The solution was applied for three days before cultures were taken. If positive cultures were then obtained, a second course of treatment was usually given. They concluded from their results that chloramine T used as a nasal douche is of definite value in the treatment of meningococcus carriers. It should be carried out, however, under personal supervision. Inasmuch as chloramine compounds do not cause albuminous precipitation in secretions, it would seem that they might find a useful place in the treatment of carriers. The value of chloramine T, however, has not

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been substantiated by other workers. Inhalation chambers as used by Kuster and automatic spraying apparatuses suggested by Gordon and Flack, in which chloramine T and zinc sulphate were used have given only fairly satisfactory results. Dichloramine T as suggested by Dunham and Dakin dissolved in eucalyptol in 2 per cent solution has also been used. It should be borne in mind that inasmuch as so many different measures cause the meningococcus temporarily to disappear from the rhino-pharynx a sufficient length of time should pass between the cessation of treatment and the taking of swabs before an individual is discharged and regarded as free from meningococci. Although there is some difference of opinion as to the value of these different local antiseptics in the treatment of meningococcus carriers, the majority of authors regard local treatment as a valueless procedure.

The specific treatment of meningococcus carriers has lately received considerable attention. This has been carried out by means of active immunization with vaccines given subcutaneously in doses of from 50,000,000 to 2,000,000,000. The injection of the vaccine used by Colebrook and Tanner gives very slight constitutional disturbances which pass off quickly. In their series five out of the ten carriers became negative and the other five cases were unaffected. The meningococcus later reappeared in the negative cases. It is scarcely to be expected that the immunization of carriers would have any effect upon the meningococci in the rhino-pharynx inasmuch as recently shown by Gates the blood serum of chronic carriers does already contain agglutinins.

Passive immunity as a prophylactic measure

The production of passive immunity by the injection of antimeningococcus serum and of active immunity by treatment with vaccines has been advocated as a prophylactic measure by a number of different workers. The experiments of Jochmann in 1906 when he produced passive immunity in animals by the use of serum suggested to him that this might be a useful measure in the prevention of the disease. With the exception of Ruppel who recommended its use in 1907, the method was not employed extensively until the 1912 epidemic in Texas. Sophian advised its use as a prophylactic measure

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among the attendants who came in direct contact with the patients with meningococcus meningitis. He recommended the subcutaneous injection of 10 to 20 cc. of serum. The dosage is necessarily arbitrary and depends on the serum used. The duration of the immunity afforded was considered one month and in Sophian's cases only one of the persons inoculated contracted the disease. He was a porter who developed meningitis six weeks after the preventive treatment. The chief objection to the prophylactic use of antimeningococcus serum is that the passive immunity conferred is only temporary. The occurrence of serum sickness and the danger of anaphylactic shock if subsequent injections of serum are necessary should not be considered as contraindications to its use any more than they are contraindications to the use of diphtheria or tetanus antitoxin provided the antimeningitis serum is an effective prophylactic. That there is doubt of this is shown by the fact that in the epidemics of the world war it was not extensively employed.

Active immunity as a prophylactic measure

Active immunization by means of meningococcus vaccines had not been used extensively before the war. It has been known for a long time that a certain degree of immunity develops during the active stage of meningitis. This has been demonstrated by complement fixation tests, by agglutination tests and by the estimation of the opsonic index. These same tests have shown that the immune bodies increase in laboratory animals after vaccination. Because of these facts and because of the analogy of meningococcus meningitis to other bacterial diseases, Sophian employed vaccination as a prophylactic measure in the epidemic in Texas in 1912. The results were inconclusive as most of the vaccinated persons did not complete the series of injections. Later Sophian and Black studied the agglutination and the complement fixation of the serum of ten students who had been vaccinated with two or three doses of a monovalent vaccine. The doses given were 500,000,000 to 2,000,000,000 organisms at seven-day intervals. Following the vaccinations severe constitutional reactions occurred. They found the agglutinin titers of the sera of their vaccinated subjects to range from 1:200 to 1:1500. Complement was fixed in serum dilutions up to 1:250. Comple-

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ment fixing antibodies were found in low dilutions in the serum of seven of these men after an interval of two years. Sophian and Black refer to Hall's experience in Kansas City in the vaccination of about 280 persons in families in which meningitis had occurred. A number of doctors and nurses were likewise vaccinated. In no instance did the disease occur subsequent to vaccination.

During the war preventive vaccine therapy was extensively employed. Greenwood believes from his experience with 4000 men inoculated twice, first with 250,000,000 to 300,000,000 and after a week with 1,000,000,000 bacteria, none of whom contracted the disease, that vaccination is a valuable prophylactic procedure. Gates using a vaccine prepared from the two main types of meningococci vaccinated 2700 soldiers at three-week intervals with 2,000,000,000, 4,000,000,000 or 8,000,000,000 cocci. He found that these doses rarely caused more than a mild reaction except in certain susceptible individuals. In the severe reactions the symptoms simulated the onset of meningitis but they lasted only a few hours. He demonstrated specific agglutinins for meningococci in the blood serum of the vaccinated men. Among the men treated by Gates two patients who had, probably, been vaccinated during the incubation period of the disease developed meningococcus meningitis. Another patient developed meningitis at a time when immunity should have been established. During a period of four months while under observation, no cases of meningitis were known to have occurred among the others who were vaccinated. Chalmers and O'Farrell working in the Soudan report somewhat similar results using much smaller doses. They began with 5,000,000 and never exceeded 100,000,000, Treadgold using 50,000,000 and one week later 100,000,000 organisms vaccinated 79 carriers, none of whom developed meningitis and Aaser gave two doses of 300,000,000 organisms each at five-day intervals to 1200 soldiers. No vaccinated soldiers developed the disease. Recently Whitmore and his colleagues, using a polyvalent lipo-vaccine, inoculated 55 men with 40,000,000,000 and 80,000,000,000 organisms subcutaneously in one or two injections. They reported that the use of such vaccines diminish the risk of reaction. In the first days after vaccination agglutination formation was observed against three of the vaccine strains. Although the evidence thus far collected

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would seem to favor prophylactic meningococcus vaccination, further studies need to be carried out, on account of the resistance to the disease which most persons possess, before it can be stated that the measure is as important in preventive medicine as is typhoid vaccination. There are no insurmountable objections to its use.

TREATMENT

Specific serum therapy has established itself by tests under such a variety of conditions and over such a long period of time that the efficacy of this form of treatment in meningococcus infections cannot be questioned. There is however a very considerable mortality, in the neighborhood of 25 per cent, even when patients are treated intelligently and energetically. It is not surprising therefore that efforts have been made still further to improve the methods of treatment.

The premeningitic stage of meningitis

It is becoming more and more evident not alone from clinical observation but as the result of experimental work that the first stage of a meningitis in all probability is usually preceded by a bacteriemia. It is generally but not invariably a transitory invasion, the bacteria disappearing as a rule from the blood stream in a very few days. While the older view, that the infection results from the direct extension of the organism through the cribiform plate of the ethmoid or from the sphenoidal or ethmoidal sinuses to the base of the brain, has not been disproven, the majority of observers are of the opinion that the meningococcus gains access to the blood stream through the upper air passages and then becomes localized in the meninges. The question then arises is it possible to recognize meninococcus infection in the premeningitic stage and if it is possible, is treatment at that stage effective. It is very difficult to answer these questions. Meningococci may be found in the blood in a certain proportion of cases of meningitis. They disappear rapidly shortly after the time of their localization in the meninges. They disappear whether antimeningococcus serum is used or not for it is very difficult, usually impossible, to cultivate them from the blood even in untreated cases after the meningitis has lasted several days. It is very likely, indeed

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most probable, that meningococci often find their way into the blood and are there destroyed and never become localized in the meninges. In these circumstances the illness would be passed over as a febrile reaction of undiscoverable origin. If blood cultures were made from such cases, as might be done in the midst of an epidemic in an army or navy, meningococci discovered and some form of therapy instituted, favorable results might be ascribed to this form of therapy which were not merited, in the same way that favorable results might be ascribed to some form of therapy in abortive cases of poliomyelitis. Furthermore there are certain cases of meningococcus sepsis in which meningeal localization never occurs. They run their course, recovery often taking place, uninfluenced by treatment.

Intravenous serum therapy

As a result of many studies during the recent war intravenous serum therapy has been warmly recommended by some authors or believed to be indicated by others. These authors are Herrick, Baeslack, Worster-Drought and Kennedy, Golden, Loch and Hebert, Hayden and others. It is maintained that the serum should be given intravenously in large doses to overwhelm the infection within the first twelve to twenty-four hours before the localization of the organism in the meninges. When meningitis has been established it is recommended that the combination of serum both intravenously and intraspinously with repeated spinal punctures should be carried out. The routine method outlined by Herrick is as follows: On admission a patient presenting the early symptoms of meningococcus meningitis is subjected to lumbar puncture. If the spinal fluid is cloudy, enough is removed to reduce the intraspinal pressure to an approximate normal and a less amount of serum is at once allowed to run into the spinal canal. If the spinal fluid is clear, no intraspinal injection is made. The fluid is immediately examined. Meanwhile the patient receives a desensitizing dose of serum. One hour later 50 to 120 cc. of serum are administered by vein, the first 15 cc. at the rate of 1 cc. per minute. Large glass syringes are used for this, as the flow is easily controlled and a cumbersome arrangement of tubes and stopcocks is not necessary. In a case of ordinary severity this intravenous dose is repeated every twelve hours until the tempera-

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ture becomes normal, or until six or eight injections have been given. In severe cases the serum is repeated every eight hours. If meningitis is present or if it subsequently develops, intraspinous injections of serum are given and repeated once in twenty-four hours until the organisms disappear from the spinal fluid and lymphocytes make their appearance in numbers. In Herrick's experience with large intravenous injections of serum combined with intraspinous treatment meningococci disappear from the cerebrospinal fluid more rapidly than when intraspinous therapy alone is employed. Herrick believes that when antibodies are present in the blood stream removal of cerebrospinal fluid allows the passage of antibodies from the blood stream into the subarachnoid space. He states that he has seen no ill effects from these large amounts of serum intravenously. In 129 cases treated by Herrick by intraspinous method alone or with small doses of serum intravenously the mortality was 37 per cent. In 79 cases treated with large amounts of serum intravenously and average amounts intraspinously it was 16.4 per cent. In 138 cases reported by Golden the mortality was 21 per cent. It cannot be denied that the intravenous injection of serum is a logical procedure when the disease is recognized during the premeningitic stage of the disease, which is infrequently the case. The diagnosis at this stage of the disease is difficult to make and except in the midst of epidemics the vast majority of the cases are not recognized before the development of the meningeal symptoms. After this there is usually no bacteriemia. It is contended that the course of the disease is shortened and the mortality is reduced by the combined intravenous and intraspinous method of treatment. Whether this is so only in cases of meningitis with an associated blood infection or applies as well to cases of meningitis without organisms cannot be proven until more data become available. The great variation in the mortality during an epidemic in cases treated by the same methods makes one regard the statistics relating to the intravenous use of serum conservatively (chart 1).

Although Herrick states that he has seen no ill effects from the use of large doses of serum intravenously, other clinicians have not had such good fortune. Golden found that the intravenous injection of 20 to 40 cc. were usually followed by more or less shock with

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failure of the pulse and respiration lasting about fifteen minutes, followed by chill and fever. The French clinicians, Sainton, Netter and Brules, while recognizing the theoretical advantage of intravenous serum, consider it a dangerous procedure and advise the use of intramuscular and subcutaneous injections. Although many writers refer to the reaction from the intravenous injection of serum, no fatal-

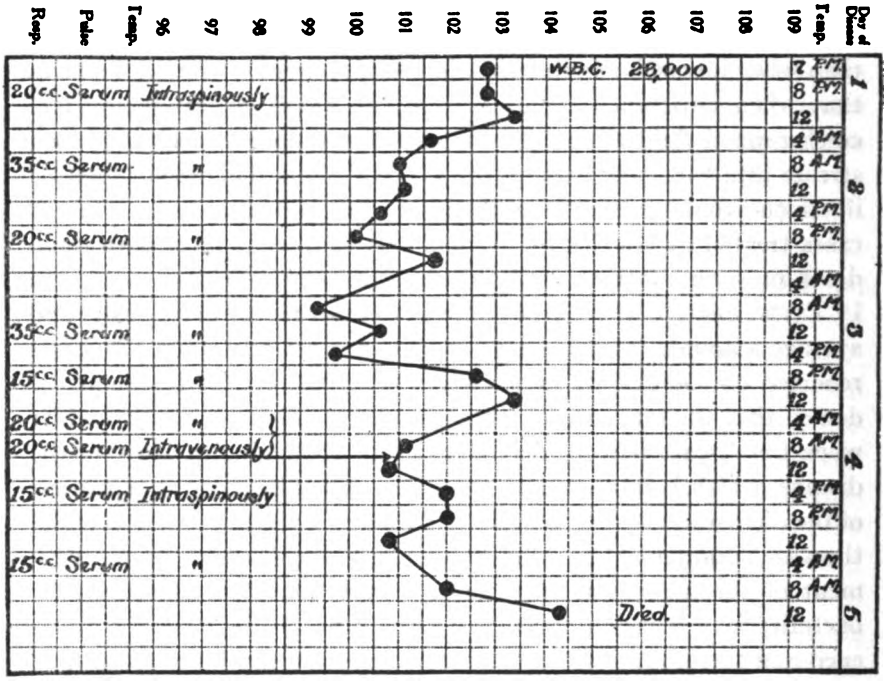

CHART I.

VERY SEVERE CASE. DEATH ON FIFTH DAY IN SPITE OF INTRASPINOUS AND INTRAVENOUS TREATMENT

ities have been recorded. I have seen two children whose death was apparently hastened by its use and for that reason I am inclined not to use serum intravenously except in specifically indicated instances. Intravenous serum therapy in meningococcemia alone or in those cases of meningitis in which the meningococcus persists or reappears in the blood stream is a rational and highly advisable procedure. A special serum freshly prepared and free from sediment

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and preservative should, however, be prepared for intravenous use. Too great care cannot be taken in properly desensitizing the patient when serum is to be administered intravenously.

The question has recently been raised as to whether a preliminary lumbar puncture should be made in all cases where meningitis is suspected on account of the danger of producing a meningitis if there be an associated septicemia. Weed and his co-workers found that in animals the removal of cerebrospinal fluid during an artificial septicemia was followed by a localization of the infection in the meninges. Wegeforth and Latham report that the cerebrospinal fluid was normal in 55 out of 93 patients in whom meningitis was suspected and in whom lumbar puncture was done. Six of these patients at the time of puncture gave as positive blood culture and 5 of them subsequently developed meningitis. They are of the opinion that the logical procedure is to treat the blood infection and to avoid spinal puncture until signs of involvement of the meninges is evident. The experimental work of Flexner and Amoss, Austrian and others also shows that the introduction of a foreign serum favors the localization of the blood infection in the meninges. This question is one of practical clinical importance in the treatment of meningococcus meningitis. It seems imperative until we have a better means of recognizing meningococcus sepsis and an entirely accurate method beside lumbar puncture of excluding meningitis not to delay early lumbar puncture so that if meningitis is present patients may receive the benefit of serum at the earliest possible treatment.

Lumbar puncture in relation to the treatment of meningitis

Although the credit of perfecting the technique of lumbar puncture and of introducing it as a method for use in clinical medicine belongs to Quincke, the procedure was first employed by Corning in 1885 who injected various drugs into the lumbar subarachnoid space to induce spinal anesthesia. Wynter in 1889 also performed lumbar puncture to relieve the cerebrospinal pressure in patients with tuberculous meningitis. The first patient on whom Quincke performed lumbar puncture was suffering from hydrocephalus which had resulted from meningococcus meningitis. Since his admirable and complete study, lumbar puncture has been adopted generally in the

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study and treatment of disease of the central nervous system. Puncture of the subarachnoid space is generally performed in the lumbar region as here the spinous processes are short and widely separated. The subarachnoid space is more spacious at this point than at the upper part of the spinal canal and there is no danger of injury to the cord. The site of election is between the fourth and fifth lumbar vertebrae, or on a level connecting the highest points of the iliac crests. At this point the subarchnoid space is entered below the conus medullaris through the comparatively thin layer of lumbar muscles. Punctures at other levels while less desirable may be made as high as the eleventh or twelfth thoracic vertebra or at the lumbosacral interspace below. Above the level of the eleventh interspace lumbar puncture is seldom successful, it may indeed be dangerous. Lusk found above this point that the posterior subarachnoid space was frequently obliterated by adhesions even in normal persons and that in this situation fluid could not be obtained unless the cord were perforated and the anterior subarachnoid space entered. From the time when Wynter in 1889 made a small incision along the spine of the second lumbar vertebra and introduced a Southey tube and trocar into the subarachnoid space many forms of apparatus, many of them elaborate, have been devised for this procedure. Simple instruments are entirely satisfactory. The needles measure from 3 to 10 cm. in length and from 0.8 to 1.6 mm. in diameter. They should be stiff but allow of a certain amount of flexibility. It should be possible readily to withdraw the stylet from the needle. The stylet should be beveled and flush with the end of the needle. The needle should have a short bevel and should be sharp so as to pass readily through the dura and not push it in front of it and thus prevent the flow of cerebrospinal fluid. Strict surgical asepsis is imperative. The needle and other apparatus should be boiled and the site of the puncture properly prepared according to the usual surgical methods. Great care should be taken to avoid secondary infection.

Lumbar puncture may be performed in either the upright or recumbent posture but in meningitis it is always the conservative plan to perform the operation in the recumbent posture. It is difficult to maintain patients in the upright position for as long a time as is necessary and there is greater danger from collapse. It is more

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convenient to puncture adults in bed. Infants and children may be moved to a firm table or surgeon's carriage. The patient is moved to the edge of the bed or table on either side with the buttocks at the edge; the knees are flexed on the abdomen and the head and neck are bended forward so that the whole spine is flexed to its fullest extent. The patient must be maintained in the required position quietly and without struggling. As the position is a matter of the greatest importance in facilitating the operation, a competent assistant is necessary. Carelessness on the part of the assistant in maintaining the patient in the proper position is the cause of more unsuccessful punctures than is lack of skill on the part of the operator. With the patient in the proper position, the lateral or the median route may be selected to enter the subarachnoid space. In either route the anatomical landmarks are the same. The puncture should be made between the fourth and fifth lumbar vertebrae at a point about on a line drawn between the iliac crests. The spinous process of the fourth lumbar vertebra is located and the needle is inserted into the interspinous space next below this. In the median route the needle is inserted directly through the interspinous ligament and dura-mater. The depth of the puncture varies from 1 inch in children to 3 inches in adults. With experience a sense of touch is developed which indicates that the subarachnoid space has been entered. The median method is preferred with children. Many clinicians prefer the lateral method in adults as the firm interspinous ligament is avoided and nothing except soft tissues are met until the ligamentum subflavum is reached. The technique for this method given by Foster and Gaskell is as follows: The needle is held with the butt resting in the hollow of the palm, the shank steadied by the forefinger and thumb. A point is then selected mid-way between the fourth and fifth lumbar spines, $\frac{1}{4}$ inch laterally to the middle line, and preferably on the dependent side. The skin is steadied by the forefinger and thumb of the left hand. The needle is pushed toward the middle line, forwards and slightly upwards. Should the needle impinge upon the bone, it must be slightly withdrawn and the point directed lower down. If no bone is encountered, the point of the needle is felt to pass through the ligamentum subflavum, which gives the sensation of piercing gristle, and then through the dura mater. The piercing of the dura

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mater has an entirely different feel, which has been described as being like passing a knitting needle through sacking. When the dura mater has been pierced, the needle can be felt free in the subarachnoid space. In either method the needle should not be pushed farther after it has pierced the dura mater, otherwise it may reach the body of a vertebra and injure one of the anterior longitudinal veins. Blood is then obtained. This is a much more frequent occurrence in children than in adults. Having entered the subarachnoid space, the stylet is removed and the cerebrospinal fluid is permitted to flow. The stylet should never be withdrawn completely until after a few drops of fluid have escaped so as to permit the cerebrospinal pressure to be lowered gradually rather than rapidly. After the first few drops the fluid for examination is collected in a sterile test tube. The amount of fluid withdrawn is determined by the rate of flow and the general reaction of the patient. Usually when the flow reaches a rate of one drop to every three seconds it indicates that about a sufficient amount has been withdrawn. The patient should be observed most carefully during this procedure. Headache, alteration in pulse and respiration are warnings that further amounts of fluid should not be withdrawn. Although Sophian has shown that the evacuation of cerebrospinal fluid in very large amount has but little effect on the blood pressure, I do not believe it is a wise procedure to withdraw the fluid completely. I have seen a number of patients suffer severe collapse by withdrawing too completely the fluid from the subarachnoid space. Manometers have been devised by Quincke, Kroenig, Crohn and others to indicate the sudden fall in cerebrospinal pressure but these are unnecessary if the pulse and respirations are watched and the fluid allowed to escape slowly and to run until it has reached the normal rate.

Lumbar puncture as a rule is a comparatively easy procedure but even in the hands of those who have developed a considerable degree of skill unsuccessful punctures occur not very infrequently, especially in infants and young children. The most common causes of failure to obtain fluid are that the needle has not been within the subarachnoid space, that it has not penetrated the dura or that it has been obstructed by a nerve. Rotating the needle or moving the needle slightly backwards or forward, reinserting and withdrawing the

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trocar often are followed by a free flow of fluid. Sometimes the fluid may be so thick that it cannot flow through the needle. In such cases it may be impossible to obtain even a few drops of fluid. Small particles of exudate may obstruct the lumen. Reinserting the trocar or moderate suction by a syringe may obviate these difficulties. Blood in the spinal fluid may be due to the puncture of a small blood vessel in the subcutaneous tissue, or an injury to a branch of the venous plexus in the spinal cavity. Blood appearing toward the end of the collection of cerebrospinal fluid may mean that there has been a rupture of the capillaries within the subarachnoid space as the result of the relief of pressure. In exceptionally fulminating cases the cerebrospinal fluid is sometimes hemorrhagic.

A successful puncture in nearly all cases is possible but many times it requires great perseverance. It is questionable whether one should speak of a so called "dry tap." I have never seen but one instance in which fluid could not be obtained and that was in a patient with a congenital obstructive hydrocephalus from whom a meningocele had been removed. Even in obstructive hydrocephalus a certain amount of cerebrospinal fluid can be obtained.

As mentioned above, too rapid lowering of the cerebrospinal pressure seldom produces symptoms of shock or collapse. Incontinence of urine and feces, sharp pains along the thighs, headache, pain and weakness in the back, etc., sometimes follow the procedure but they are usually temporary. As in the case of lumbar puncture for spinal anesthesia, temporary paralysis of the bladder and anus and even paraplegias have been described following lumbar puncture and the introduction of serum. It is difficult in meningitis to account for these sequelae entirely as the result of lumbar puncture. The dangers from lumbar puncture itself are remote and for the most part with proper precautions may be disregarded.

As it is necessary during the course of the disease to make repeated punctures from day to day and often over a long period of time, the interspace entered should be varied from one puncture to another and every precaution taken to prevent secondary infection. With sterile technique the skin wounds seldom become infected.

The question of anesthesia during lumbar puncture has received considerable attention both in this country and in Europe. Some

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authorities regard a general anesthesia as unnecessary while others advise either the use of a local or general anesthesia in all cases. Sophian regards general anesthesia as dangerous while Horder, Robb and others recommend its use in all cases unless the patient is unconscious or it is definitely contraindicated. A general anesthesia is to be preferred to local anesthesia as the discomfort of inserting the lumbar puncture needle as a rule is no greater than is that from the needle puncture used to inject the local anesthetic. The chief argument against a general anesthesia is that it further increases the dangers from the disease and as the discomfort from puncture is not excessive it is unwarranted with a procedure no more painful than lumbar puncture. With a patient who is delirious and struggling it is necessary, otherwise it would be impossible to keep the patient quiet and in position long enough to carry out the necessary treatment. Anesthesia may also be advantageously used with some patients who have to be repeatedly punctured on account of the fear of the operation. Anesthesia affords a sufficient amount of mental and physical relief to some adults to warrant its use but as a general rule the operation is accompanied by so little pain that it is not necessary. It is seldom necessary in infants and young children. Ether is probably the best and safest anesthetic to use.

The intraspinous administration of serum in meningitis

The successful treatment of meningococcus meningitis depends upon the early recognition of the disease and upon the early and efficient administration of antimeningococcus serum. It is essential that the serum should be of high potency and contain antibodies specific for the causative type of organism; that it be maintained within the cerebrospinal system at high concentration and in direct contact with the meningococci. Free drainage should be obtained from time to time by spinal puncture. There are also certain general and symptomatic measures that must be carried out in addition to the specific serum treatment.

Action of the serum

The chief action of the serum is doubtless due to bacteriolysins which destroy the organisms and in part also to those substances which

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promote phagocytosis. For these reasons it cannot be too much emphasized that the serum used in the treatment of a given case of meningococcus meningitis must contain antibodies specific against the infecting strain of meningococcus. By examination of the cerebrospinal fluid in the course of treatment it is appreciated that the direct action of antimeningococcus serum is on the meningococci. These become reduced in number and become altered in size and staining property. They are more readily taken up by leucocytes and their growth is inhibited. The toxic products liberated by the death of meningococci are perhaps neutralized by the antiendotoxin in the serum if such a substance be found in the serum. The extracellular organisms diminish rapidly so that after the first or second injection of serum they are almost all intracellular, gradually they disappear altogether from stained smears. The viability of the organism also diminishes so that it is impossible to cultivate them. Sometimes even when seen in smears, they fail to grow on culture media. Levy has shown that the meningococcus disappeared from the cerebrospinal fluid in 114 cases after the intraspinous injection of serum as follows: After the first injection of serum it disappeared in 18 cases, in 33 after the second injection, in 35 after the third injection, in 14 after the fourth injection, in 9 after the fifth injection, in 4 after the sixth injection and in 1 after the eleventh injection. I found that in the majority of cases the meningococci disappeared after five injections of serum. In the following summary the number of injections of serum required to destroy the meningococcus as shown by culture and smears:

In 5 cases the organism disappeared after 1 injection
In 4 cases the organism disappeared after 2 injections
In 7 cases the organism disappeared after 3 injections
In 4 cases the organism disappeared after 4 injections
In 9 cases the organism disappeared after 5 injections
In 2 cases the organism disappeared after 6 injections
In 1 case the organism disappeared after 7 injections
In 1 case the organism disappeared after 9 injections

As the result of the reduction in number and the disintegration of the meningococci and the diminution in the number of leucocytes, the turbid or purulent cerebrospinal fluid gradually becomes clear.

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But aseptic meningitis which may be caused by the introduction of a foreign serum may be sufficient to cause a certain amount of turbidity in the fluid until treatment is discontinued. The polymorphonuclear cells are finally replaced by mononuclear cells at first in increased number and eventually these are reduced within normal limits. At the same time the globulin content in the cerebrospinal fluid and the amount of cerebrospinal fluid diminishes progressively from day to day. The fluid in cases recovering from cerebrospinal meningitis may closely simulate, with the exception of the presence of bacilli, that found in tuberculous meningitis. It may be increased in amount and clear but may contain an excess of mononuclear cells and globulin and may even form a film on standing. It may require days or even weeks before the fluid becomes normal. Besides acting directly on and destroying meningococci and neutralizing the endotoxins liberated, antimeningococcus serum undoubtedly hastens the solution of the exudate.

Antimeningococcus serum should be injected directly into the subarachnoid space. The subcutaneous and intramuscular injection of serum in meningitis is valueless. Previous to the introduction of the gravity method by Heiman in 1908, serum was introduced into the meningeal spaces by means of a syringe. After the cerebrospinal fluid was withdrawn the syringe was attached to the lumbar puncture needle and the serum injected slowly and with very little pressure. The gravity method is the one of choice, however, as the serum runs in slowly and at a regular rate with no sudden and pronounced increase in intracranial pressure. The cerebrospinal pressure may be directly controlled by raising or lowering the level of the fluid in the gravity apparatus. Elaborate equipments for the introduction of serum by this method may be obtained but for practical purposes it is only necessary to have a graduated funnel with rubber tubing which is connected with the lumbar puncture needle by a close fitting metal attachment. After the cerebrospinal fluid has been withdrawn the attachment is made and the serum, which has been warmed to body temperature, is allowed to run from the graduated cylinder into the subarachnoid space, care being taken that all air has been expelled from the tubing. The rapidity of flow is regulated by raising or lowering the funnel.

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Symptoms caused by the injection of serum

The injection of serum invariably causes severe, often agonizing cramp-like pains which radiate down the back of the legs, to the epigastrium or up the back. These pains usually begin as soon as the serum flows in and are due to the sudden rise in pressure and stimulation of the nerve roots. They can be lessened somewhat by allowing the serum to run in at first very gradually. Serum warmed to body temperature before injection causes less pain than when it is cold. The pains disappear shortly after the cessation of the injection and often before it is terminated. After the serum has been injected the stylet should be replaced and the needle left in place. By following this routine procedure the cerebrospinal pressure can be quickly lowered if any serious disturbances develop from the injection. After a few minutes the needle is withdrawn and the wound closed with a sterile dressing. It is advised that the foot of the bed be elevated in order to facilitate the flow of serum to the cerebrum and that the patient lie on his face so that the serum will be directed to the region of the optic chiasm. As it has been shown that dyes when injected into the lumbar subarachnoid space pass upward within a few minutes and are quickly distributed over the brain, these measures are not absolutely necessary.

Sophian in observations on patients and Carter in experiments on dogs have shown that the symptoms of collapse which fortunately are not frequently met with are due to a sudden increase of intracranial pressure and a resulting depression of the respiratory center. This sudden increase results from a too great pressure used in the injection of the serum, too rapid an injection or too large a quantity of fluid injected at one time. The first sign of danger is an alteration in respiration, the breathing becoming slow, shallow and irregular. Respiration may suddenly cease. Dilatation of the pupils and incontinence of urine and feces also occur. The heart continues to beat for a long time. In one of my patients to whom serum was being given by the syringe method the respiration ceased but the heart's action continued actively for over an hour. Lowering the intracranial pressure by removing some of the serum that had been injected and active respiratory stimulation were unavailing. Sophian

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recommends that the injection of serum should be controlled by blood pressure readings and that a drop of 20 mm. of mercury in the blood pressure of an adult is a contraindication to the further injection of serum. This procedure may advantageously be used in adults but with children in whom blood pressure determinations at best are variable, it is unsatisfactory. By the use of the gravity method, allowing ten to twenty minutes for the serum to run into the cerebrospinal space, alternately raising and lowering the funnel so that the flow of serum is carefully regulated and watching the patient closely for signs of impending relapse, the dangers of intraspinous treatment are materially lessened. Should signs of collapse appear, the injection should be stopped at once, the apparatus disconnected and the serum allowed to drain out. Artificial respiration should be started and atropine and adrenalin should be injected in full doses. In animals Carter showed that the symptoms could be relieved immediately by the injection of cocaine.

Dosage of serum

Inasmuch as the serum acts directly on meningococci, the important indication is to inject as much serum as is consistent with safety. As there is no standard measurement of activity of the serum and as it is not known accurately how much serum is necessary to destroy the organisms and neutralize their effects, the dose is measured by volume. The chief objects of the intraspinous treatment are to relieve the intracranial pressure, to remove the infectious cerebrospinal fluid and to inject the bactericidal serum so that it comes into direct contact with the meningococci. It is the custom of nearly all clinicians to inject a smaller amount than the quantity of cerebrospinal fluid withdrawn. If 45 cc. of cerebrospinal fluid are withdrawn, it has been regarded as safe to inject 30 cc. of serum. In this way it is thought that there is no danger of increasing unduly the intracranial pressure. While in general this is a relatively safe rule to follow, it cannot be sufficiently emphasized that the injection must be made slowly and even when these precautions are observed, patients are occasionly met with in whom alarming symptoms result from the introduction of even small amounts of serum. As the result of Sophian's experience in controlling the dosage of serum by blood

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pressure readings together with the clinical experience of many other observers, the following arbitrary standard of dosage according to the age of the patient may be generally considered safe:

1 to 5 years	5 to 15 cc.
5 to 10 years	10 to 20 cc.
10 to 20 years	20 to 30 cc.
20+ years	30+ cc.

However, it should be borne in mind that the dosage varies with each individual patient and that the volume of serum introduced should never be greater or as great as the amount of cerebrospinal fluid withdrawn. It is far better to inject an inadequate amount of serum and repeat the injection with no harm to the patient than to inject a larger dose with serious consequences.

In patients with thick plastic exudates and in those in whom only a few drops of cerebrospinal fluid can be obtained, the injection of small amounts of serum at frequent intervals, even under a certain amount of pressure, is compulsory for in no other way is it possible to introduce the serum and the danger of introducing serum in this way is less than allowing the patient to go untreated. In patients with a very thick cerebrospinal fluid which will not flow through the needle, two needles may be inserted at different levels and the canal irrigated with sterile salt solution. This sometimes sufficiently dilutes the cerobrospinal fluid as to allow it to flow and so permits the injection of larger doses. But even if free drainage can be established by repeated intraspinal injections the process is time consuming and irremediable damage, such as obliteration of the foramina between the ventricles and the cerebrospinal space, may be done in the meantime. Moreover, a very thick exudate means a very severe inflammatory process, the presence of a very large number of organisms and an urgent demand for early and intensive treatment. Intraventricular treatment is under these circumstances clearly indicated. The method of accomplishing this will be described subsequently.

An instructive example of what may be accomplished under such conditions are afforded by the following case:

The patient, three months of age, was admitted to the Harriet Lane Home on the third day of the disease, with a history of vomiting, fever, restless-

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ness and convulsions. On physical examination there were the characteristic signs of acute meningitis and several small petechiae on the face. The temperature was 101.6°. As no cerebrospinal fluid could be obtained by lumbar puncture, a ventricular puncture was immediately done. The cerebrospinal fluid was cloudy and contained many polymorphonuclear leucocytes and numerous intra- and extra-cellular Gram-negative diplococci. The meningococcus was grown in culture. The blood culture was negative. Twenty cubic centimeters of serum were injected into the ventricle at once. Twelve hours later a few cubic centimeters of thick, turbid fluid showing meningococci were obtained by lumbar puncture. Five cubic centimeters of serum was injected under pressure with a syringe. On the following day, thirty cubic centimeters of serum was injected into the ventricle and although only a few cubic centimeters of cerebrospinal fluid was obtained by puncture, five cubic centimeters were again injected into the lumbar subarachnoid space by a syringe. At the time of the second lumbar puncture the spinal canal was irrigated with sterile normal salt solution but this did not have an effect on the amount of fluid which could be obtained. Phenolsulphonephthalein injected at this time into the lumbar subarachnoid space had not appeared in the ventricles the following morning. Thereafter thirty cubic centimeters of serum was injected into the ventricle and five cubic centimeters of serum was injected with a syringe into the lumbar subarachnoid space every twenty-four hours. The amount of cerebrospinal fluid removed by lumbar puncture slowly increased and after the seventh day thirty cubic centimeters of fluid was obtained. Phenolsulphonephthalein at this time flowed freely from the ventricle. The meningococci disappeared.

Frequency of injection

The frequency with which antimeningococcus serum is to be injected depends upon the severity of the infection and the duration of the infection before treatment is instituted. In a suspected case of meningitis lumbar puncture should be performed and if a cloudy fluid is obtained antimeningococcus serum should be administered without waiting for a bacteriological examination. Should the case eventually be shown not to be due to the meningococcus, no harm will have been done. In cases of average severity when seen within the first two or three days after the onset, the injection should be repeated every twenty-four hours for three or four doses. Hoher, Dochez, Debre and others have demonstrated that the serum is

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practically all absorbed within twenty-four hours. No greater interval of time should therefore elapse between treatments. In cases of greater severity the injection should be repeated every eight or twelve hours for three or four doses and thereafter every twenty-four hours. This is for the reason that the activity of the serum may be exhausted in a short period of time even before the fluid portion of the serum is absorbed. The appearance of the cerebrospinal fluid at each puncture, the number of organisms and their relationship

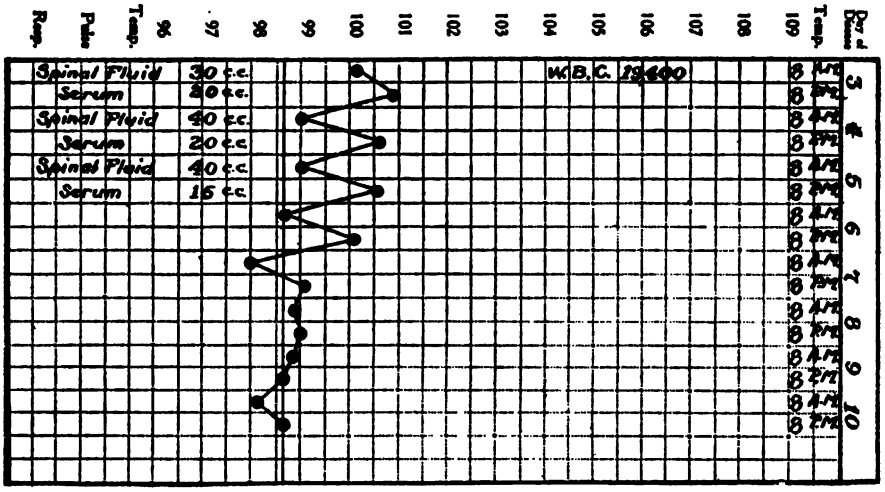

CHART II.

MILD CASE OF MENINGOCOCCUS MENINGITIS REACTING PROMPTLY TO INTRASPINOUS INJECTION OF ANTIMENINGOCOCCUS SERUM

to the leucocytes and their ability to grow upon proper culture media together with the general condition of the patient are the only safe and reliable indications to follow as to the frequency with which serum is administered.

Discontinuance of serum

In the average uncomplicated case of meningococcus meningitis, serum treatment is discontinued when the cerebrospinal fluid becomes clear and the organisms can no longer be demonstrated in smears or in culture. By this time also there is a general improvement in the

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condition of the patient and the fever has usually nearly disappeared. With serum treatment the average duration of active symptoms is from eleven to fourteen days.

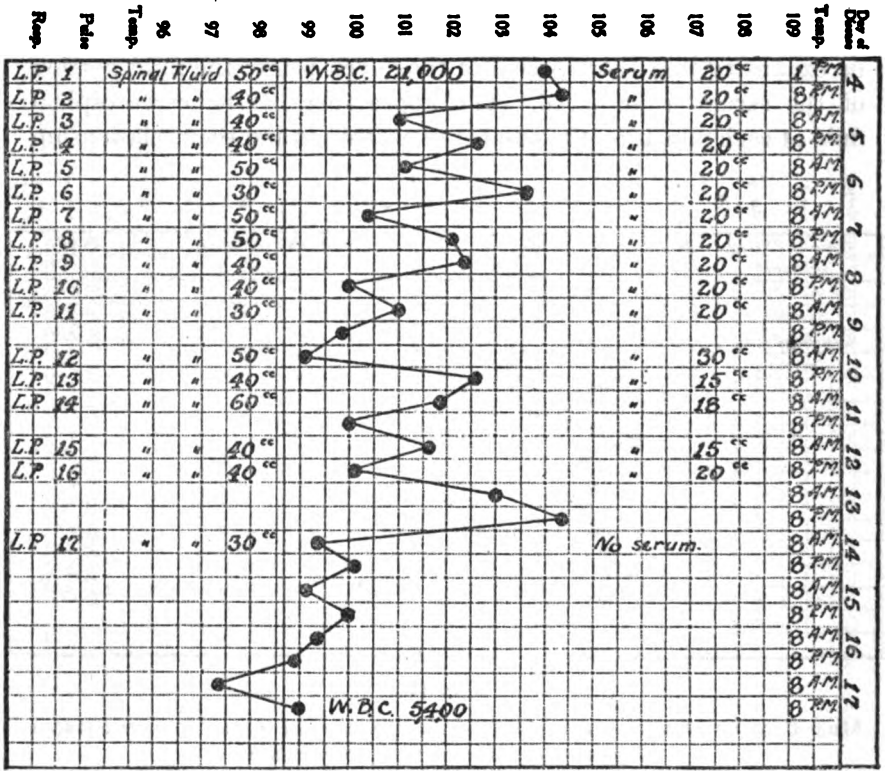
Resp.
Pulse
Temp.
L.P. 1 Spinal Fluid 50 cc
L.P. 2 " " 40 cc
L.P. 3 " " 40 cc
L.P. 4 " " 40 cc
L.P. 5 " " 50 cc
L.P. 6 " " 30 cc
L.P. 7 " " 50 cc
L.P. 8 " " 50 cc
L.P. 9 " " 40 cc
L.P. 10 " " 40 cc
L.P. 11 " " 30 cc
L.P. 12 " " 50 cc
L.P. 13 " " 40 cc
L.P. 14 " " 60 cc
L.P. 15 " " 40 cc
L.P. 16 " " 40 cc
L.P. 17 " " 30 cc
W.B.C. 21,000
W.B.C. 5400
Serum
" 20 cc
" 30 cc
" 15 cc
" 18 cc
" 15 cc
" 20 cc
No serum.
Temp.
Pulse
Resp.

CHART III.

THIS PATIENT REQUIRED INTENSIVE AND PERSISTENT INTRASPINOUS TREATMENT

The spinal fluid, which would become apparently clear at one puncture, would at the next be very turbid and filled with organisms. Sixteen intraspinous treatments were required with a total injection of 320 cc. of serum before the spinal fluid became clear and meningococci disappeared.

Unfortunately the indications are not always definite and it requires sound judgment in determining when the injections are to cease. Although the general clinical condition of the patient as a rule may be relied upon as an indication, one often sees patients who are apparently recovering but viable organisms persist in the cerebro-

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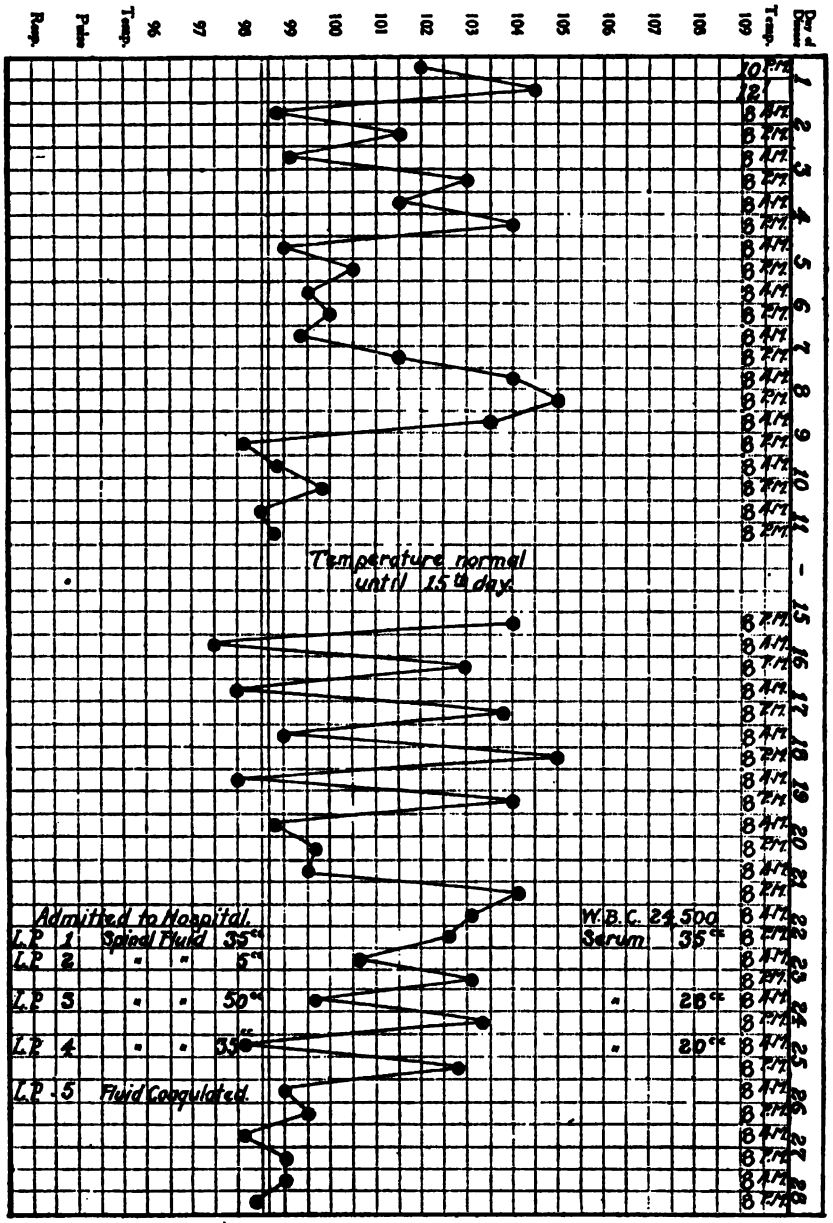

CHART IV.

CHARACTERISTIC FEBRILE REACTION IN AN UNTREATED CASE

While serum therapy is usually not very effective late in the course of the disease, it may at times bring about rapid cure. This patient was ill twenty-two days with an obscure fever, the cause of which had not been recognized. The temperature record had been kept. After 3 intraspinous injections of serum the patient made an uninterrupted recovery.

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spinal fluid. The reverse is also often true. The patient may remain unimproved with persistence of the signs of meningeal irritation and yet the organisms cannot be demonstrated in the cerebrospinal fluid. The fever as a rule subsides with the disappearance of the organisms but it should also be remembered that irregular febrile paroxysms may often be caused by the injection of the foreign serum and in prolonged cases by the development of serum sickness. The only reliable criterion for the discontinuance of serum treatment is the disappearance of the organisms from the smears of the cerebrospinal fluid and their failure to be cultivated upon proper media. As the meningococcus grows slowly upon media it requires two or three days to be sure that a growth will not take place. When treatment is employed once in each twenty-four hours, two or three injections have thus been made after the cerebrospinal fluid is free from viable organisms. This is an added safeguard and produces no unfavorable effects. After that the character of the cerebrospinal fluid is followed by lumbar puncture at irregular intervals. Repeated lumbar puncture serves a double purpose in permitting cytological examination of the cerebrospinal fluid and relieving the increased intracranial pressure which frequently follows meningococcus meningitis.

Turbidity of the fluid is not an unfailing criterion for the continuation of treatment. The fluid may be free from organisms and yet contain so many cells as to be definitely cloudy or "ground glass" in appearance. The recent studies of Weed and his collaborators have shown the influence of the injection of foreign serum in bringing about such changes.

Early intraventricular injection of serum

In a series of articles which have recently appeared, Lewkowitz in discussing the serum treatment of meningococcus meningitis concludes that inasmuch as the lateral ventricles are the principal and essential seat of the infectious process, the meningococci spread from this focus throughout the entire subarachnoid space. He advises therefore that the serum should be injected into the lateral ventricles at the beginning of treatment and that daily injections in alternate sides or simultaneously on both sides should be made. In addition he recommends the use of vaccines. He describes the

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method: The skull is punctured with a Götze grooved hand drill, 1.5 mm. wide. The needle is 1 mm. in diameter and 7 or 7.5 cm. long. A brass guide inside the needle prevents obstruction with tissue. The tip of the needle is not sharp, as the only obstacle it has to force is the dura. The puncture is made anywhere along the top of the skull, 3, 4 or 5 cm. from the median line, pointing the tip of the needle toward the center of the skull. The depth of the puncture should be about 40 mm. for infants, 50 to 60 mm. for older children, and 60 to 75 mm. for adults. The fluid should not be injected until the needle is certainly in the ventricle. This is proved by the fact that cerebrospinal fluid flows from the needle and by the drop in tension as the antiserum spreads in the ventricles. The tension should not surpass 60 to 80 mm. mercury for older children and adults, and 40 to 50 for infants. Lewkowitz advises therefore that a manometer with a three-way stopcock be interposed between the needle and the syringe. The injections are always made through a new opening. In the first series of cases which he reported the mortality was 36 per cent and this rather high mortality he accounts for on the basis of an inactive serum and fulminating types of cases. He warns against the use of horse serum for a period longer than 13 days on account of an anaphylactic reaction in one case. After the thirteenth of fourteenth day he is inclined to rely on the use of vaccines. He believes that all cases should be treated by the early ventricular injection of serum. Undoubedly this would be the procedure of choice were it definitely established that the organism gained entrance to the meninges by way of the ventricles. The weight of evidence in meningitis produced experimentally is against this view. Although the intraventricular injection of serum has its indications in small infants and in patients with a thick plastic exudate with or without hydrocephalus, the early injection of serum into the ventricles in the average uncomplicated case is not necessary.

Amount of serum used during the treatment

The amount of serum required in each individual case varies within wide limits and depends entirely upon the course of the disease. In one of my patients who was treated four hours after the onset of meningeal symptoms, only one injection of 20 cc. of serum was given

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and was followed by rapid recovery. Netter, Worster-Drought and Kennedy and others have given as high as 600 to 800 cc. during the course of the disease without ill effects. It is not so much the amount of serum that is important as it is the quality of the serum and the time at which it is employed (chart V).

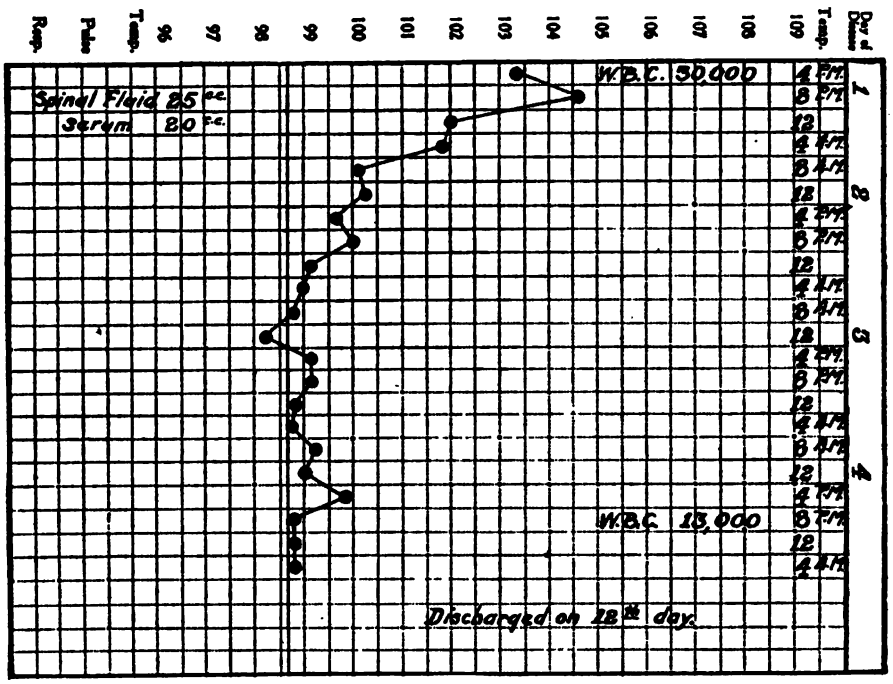

CHART V.

FIRST AND ONLY INJECTION GIVEN FOUR HOURS AFTER ONSET

Cerebrospinal fluid clear, containing many Gram-negative extracellular organisms. Complete recovery.

REINFECTION AND RELAPSES

The reappearance of meningococci in the cerebrospinal fluid either with or without the appearance of signs of meningeal irritation may take place even while serum is being given or after the discontinuance of treatment. These relapses are not nearly so frequent since the introduction of serum therapy but they occur in a small proportion of patients. Worster-Drought and Kennedy observed a relapse in less than 5 per cent of their cases. In my experience they have been

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met with only in the cases running a chronic course and in the cases above referred to. They probably result from the fact that a certain number of organisms are walled off in patches of exudate which the serum cannot penetrate or else are contained in small superficial abscesses in the brain or cord. It is not always easy to recognize the beginnings of a relapse for it may occur with the onset of serum sickness and there may be strikingly few meningeal symptoms. A positive and early diagnosis of a relapse is only to be made by an examination of the cerebrospinal fluid. The treatment of a relapse is the same as the treatment of the original disease. The dangers from anaphylaxis in the treatment of relapse are considered under the heading of anaphylaxis.

During the course of meningitis there are certain symptoms that are in all probability the result of increased intracranial pressure or at least they are made worse by the pressure. These are headache, often agonizing in character, vomiting, retraction of the neck and some elevation of temperature. The mere removal of cerebrospinal fluid often brings about a distinct amelioration. These symptoms may be present sometimes to a marked degree, even after all meningococci have been killed and the serum treatment discontinued. They apparently depend upon the disproportionate production of cerebrospinal fluid due to a too rapid production or to a too slow absorption. The disease itself and the treatment by foreign serum may each be responsible for this condition of affairs. A rapid improvement results from lumbar puncture and the withdrawal of fluid but the symptoms may return again and again. It is imperative to continue the withdrawal of fluid until there is no return of any of the symptoms. This may require occasional lumbar puncture for several weeks. The following illustrates the results of repeated lumbar puncture after discontinuance of serum treatment (chart VI).

W. G., white, aged three years. Patient was admitted on the fifth day of the disease with typical picture of meningitis of severe form. Twelve intraspinous treatments with serum were given in the eight days following admission. No organisms were seen in smears from the spinal fluid after the ninth puncture. In spite of the apparently clear fluid he did not improve, the retraction of the head and the hyperaesthesia persisted, he was extremely restless and there was a coarse tremor of the extremities.

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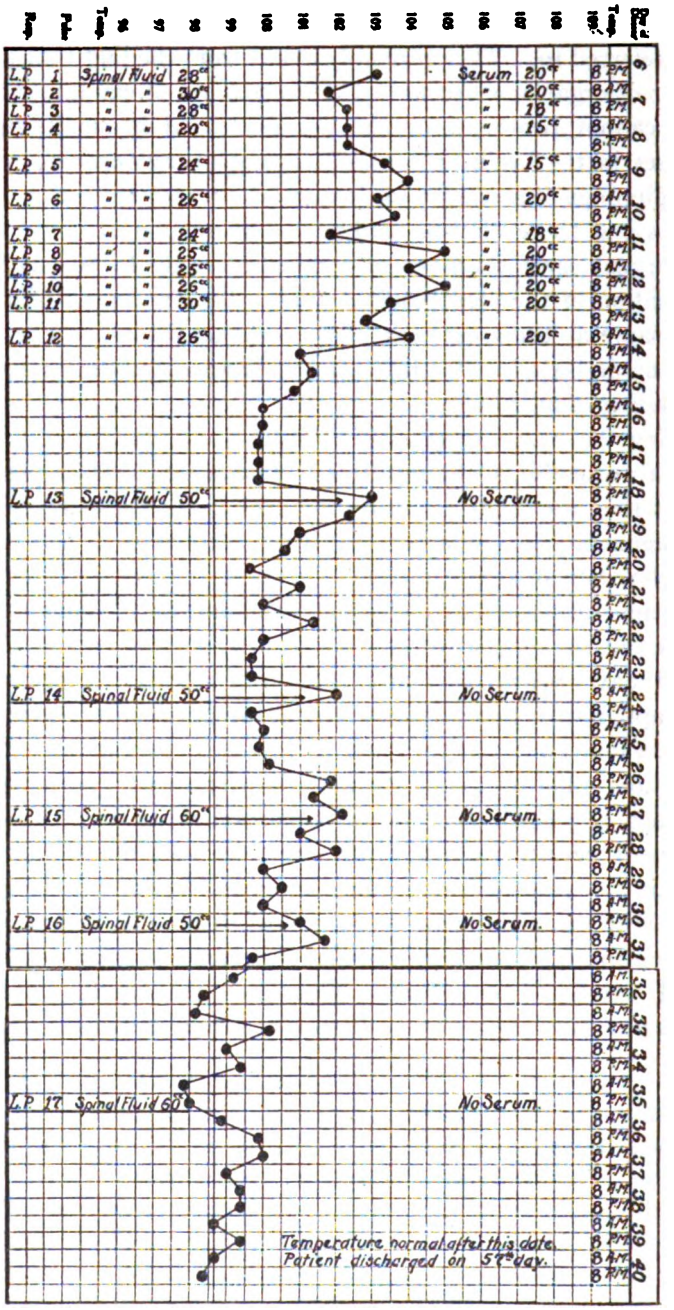
L.P. 1 Spinal Fluid 28°
L.P. 2 " " 30°
L.P. 3 " " 28°
L.P. 4 " " 20°
L.P. 5 " " 24°
L.P. 6 " " 26°
L.P. 7 " " 24°
L.P. 8 " " 25°
L.P. 9 " " 25°
L.P. 10 " " 26°
L.P. 11 " " 30°
L.P. 12 " " 26°
Serum 20°
" 20°
" 18°
" 15°
" 15°
" 20°
" 18°
" 20°
" 20°
" 20°
" 20°
L.P. 13 Spinal Fluid 50° No Serum.
L.P. 14 Spinal Fluid 50° No Serum.
L.P. 15 Spinal Fluid 60° No Serum.
L.P. 16 Spinal Fluid 50° No Serum.
L.P. 17 Spinal Fluid 60° No Serum.
Temperature normal after this date.
Patient discharged on 5th day.

CHART VI.

REPEATED LUMBAR PUNCTURE AFTER DISCONTINUANCE OF SERUM TREATMENT

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The eye grounds were normal. On the twelfth day the temperature rose to 103° and all the symptoms were exaggerated. A lumbar puncture was done and a large quantity of clear fluid containing no organisms spurted out under greatly increased pressure. There was marked relief following this procedure and the temperature fell. Thereafter, at intervals of about one week it was necessary to repeat the treatment. The symptoms were relieved each time by the removal of a large quantity of clear fluid. He was discharged as well on the fifty-seventh day of the disease.

Every one with experience in the treatment of meningococcus meningitis has seen alarming symptoms follow the injection of antimeningococcus serum. Death at times has followed treatment with serum so promptly that it is apparent that the treatment rather than the disease has been responsible. A number of views have been held as to the cause of these accidents. It has been claimed that the deaths were due to rapid lysis of the meningococcus and the consequent liberation of a toxic amount of bacteriotoxin, to the production through the introduction of large amounts of a foreign protein of anaphylactic shock, and to increased intracranial tension due to the too rapid or too free use of the antiserum. In 1912, Kramer advanced the view that cases of sudden death might be due to the presence in the serum of tricresol. Kramer injected a mixture of antimeningitis serum and a 0.5 per cent tricresol solution into the region of the fourth ventricle and directly into the subarachnoid space in dogs and as the result respirations were temporarily checked. One of the animals died after the injection of the serum into the subarachnoid space. Hall as the result of experiments also believed that tricresol is a dangerous preservative for serum which is to be introduced into the subarachnoid space and so come directly into contact with the nervous centers. He stated that death from the introduction of serum may result either from an increase in intracranial tension or from the presence in such serum of tricresol.

Flexner does not believe that the tricresol in antimeningococcus serum is responsible for the sudden deaths which have followed the use of serum. He points out that such deaths have been reported by Dopter using a serum which contained no preservative, also that there is no relationship between the conditions of the experiments and the conditions occurring in the subdural injection in human

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beings, and that the injection of serum directly into the ventricle is not followed by serious symptoms. It is his belief that the alarming symptoms and death are most probably due to a rapid increase of the intracranial pressure occasioned by the injection of serum. That they can be avoided to a great extent by careful technique is evident from the experience of Sophian who reports some 1500 injections without a serious accident.

IMMUNITY CONFERRED BY ATTACK OF MENINGITIS

The degree of immunity conferred by meningococcus meningitis is apparently very small. Worster-Drought and Kennedy were able to demonstrate agglutinins in only 3 of 39 patients who had recovered from the disease. Authentic cases are reported in which "second attacks" occurred as early as 33, 45 and 73 days and as late as four and eleven months after the primary attack. It is probably better to consider such cases as relapses rather than second attacks. Although second attacks are rare, they do undoubtedly occur.

THE USE OF MONOVALENT OR POLYVALENT SERA

Since the recognition of the different types of meningococcus and the preparation of monovalent as well as polyvalent therapeutic sera, the procedure which is advised in the routine treatment of suspected or a proven case of meningitis has varied according to the experience of different writers. All are in accord that in a case of suspected meningitis if turbid or cloudy cerebrospinal fluid is obtained by lumbar puncture that a polyvalent serum should be administered pending the results of the bacteriological report. Whether treatment should be continued with a polyvalent serum of a monovalent serum is still the subject of much discussion. French observers at one time favored the injection of 20 cc. of antiserum A with 30 cc. of antiserum B until the type of the organism could be determined. Recently Nicolle, Debains and Jouan have prepared a bivalent serum made with organisms A and B, for immediate use prior to a bacteriologic diagnosis. After this they have advised the use of a monovalent serum according to the type of the infecting strain of meningococcus. In England a similar routine has been carried out and

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as type I and type II are the most prevalent, a serum representing these two strains of meningococcus has been given at the first injection and after the causative strain has been determined, the corresponding monovalent serum has been given. The objection to the use of only bivalent serum is obvious. If there is difficulty in typing the organism a delay in using a highly potent serum might arise. But excellent results from the use of a monovalent serum have been reported from both England and France. The routine followed by Gordon and Hines is as follows: A bivalent serum made from type I and type II is used until the type of the infecting meningococcus is determined. Then the corresponding serum for the type of meningococcus found is given. Out of 83 cases, 34 were due to type I and the mortality was 3 per cent; 32 were due to type II and the mortality was 21.9 per cent. Ten were due to type III, no deaths, and 7 to unknown types and the mortality was 28.6 per cent. Out of the 83 cases the mortality was 12 per cent. The monovalent serum for type II is less effective than the sera for the other types for Gordon and Hines say that it contains less antiendotoxins for the homologous meningococcus than the other sera do. Sir Humphrey Rolleston observed a small outbreak of 10 cases due to type II. All of the patients died although treated vigorously both intravenously and intraspinously with a monovalent serum from type II organism. Munro used a pooled serum containing 50 per cent of antibodies to type II and a monovalent serum was used after the type was determined. He treated twelve consecutive cases of cerebrospinal fever in this manner and he says that in his experience no patient has died where it was possible to treat by monovalent serum. Recently a polyvalent serum has been used in this clinic in a few cases at the initial injection and thereafter the corresponding monovalent serum. The results so far have been sufficiently satisfactory but the number of cases treated have been too few from which to draw conclusions.

If it can be proved that the activity of a monovalent serum against the corresponding type of the meningococcus is greater than the activity of a polyvalent serum against the same organism, then it would seem logical to employ the monovalent serum after the type of organism has been determined. Unless this can be proved, there are great advantages in using the polyvalent serum. Studies from

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the Hygienic Laboratory in Washington have shown the titre of the polyvalent sera to be as high as that of the monovalent sera that have been tested. At present therefore it would seem that for general use a polyvalent serum is preferable.

In all cases of meningococcus meningitis the type of organism from the cerebrospinal fluid should be determined by agglutination tests and a serum containing antibodies specific for that type of organism should be used. If the types of organism used in the preparation of the serum are not known, the agglutinating power of the serum toward the specific type of organism should be tested. Sera showing a low agglutination titre should not be employed. It is the universal opinion that the polyvalent serum prepared by the Rockefeller Institute has given better results than sera prepared at other laboratories. On account of the practical difficulty in making prompt and accurate type diagnoses, all antimeningococcus sera sold in interstate traffic in the United States are now required to be polyvalent with high titre against strains representing four different serological groups. These groups roughly correspond to those of Gordon, but are not perhaps identical with them. Sera now being made in the United States are from horses which have received intravenous injections of living meningococci. At least twelve different strains representing different types and variants sent out by the Hygienic Laboratory are used in its production.

DRUGS IN TREATMENT OF MENINGITIS

Drugs, except for the relief of symptoms, have proved valueless. Hexamethylenetetramine (Hexamine) since it was shown by Crowe to be excreted into the cerebrospinal fluid has been used extensively but apparently it has no influence upon the course of the disease. In 1914, Thomas Walker suggested the use of hexamethylenetetramine-anhydromethylene-citrate (Helmitol) as a substitute for hexamine inasmuch as it liberates formaldehyde in alkaline as well as in acid media. It has been shown that this drug exerted an inhibitory effect on the meningococcus in vitro and as a result of these experiments the drug was tried in the treatment of meningococcus meningitis. Given intravenously hemitol appears in the spinal fluid within half an hour and 15 grains administered by mouth could be demon-

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strated in the cerebrospinal fluid within twenty-four hours. It was impossible, however, in any of the cases in which it was used to demonstrate the presence of free formaldehyde. Clinical results with this drug have been very unsatisfactory. Fairly and Stewart combined hemitol with normal saline or horse serum and injected this in 10 cases of meningococcus meningitis. Six of the 10 patients recovered. Besides the administration of hexamine and hemitol intravenously the arsenical preparations together with soamin have also been employed intravenously but without appreciable effect on the course of the disease. Soamin has been used principally in the East and was tried in meningococcus meningitis inasmuch as it has been thought to be of value in trypanosomiasis. Shiroore and Ross and Gilks and Butler have used the drug in British East Africa quite extensively. They reported its use by intramuscular injection in 127 cases. The mortality was over 50 per cent. Iodide of potassium and mercury and antimonium tartrate likewise have been used but without effect. The results reported by all writers show that there is little clinical or experimental evidence at hand to support the use of drugs in the treatment of this disease and they cannot be recommended unless combined with the use of antimeningitis serum.

OTHER MEASURES EMPLOYED IN TREATMENT

In the literature one finds, constantly, reference to other methods of treatment than the use of the specific serum. These methods have been tried either alone or in combination with serum. It is rather confusing to determine exactly the effects of these various added methods of treatment for the observations have not been sufficiently accurate or extensive to permit of a comparison between the cases treated with serum and those in which a combination of methods has been employed. It is an interesting commentary that even in spite of a proved specific therapy methods which have been discarded and regarded as valueless should be taken up from time to time and that beneficial results should be claimed for them. This, however, is constantly occurring in the treatment of other diseases besides meningitis.

Recently one of the earliest methods of treatment, venesection, has been revived. Fairly and Stewart contend that in the acute

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cases in which there are symptoms of respiratory failure, venesection combined with the application of cold compresses is beneficial. They also caution against the use of lumbar puncture in comatose patients, particularly if respiratory failure is imminent.

Long before the days of serum treatment various antiseptics were recommended and used intraspinously. In 1902 Seager recommended the use of lysol as a means of combating the disease and in 1904 Manges tested its effects upon a number of patients. Wolff as a result of the recovery of 5 out of 8 patients whom he treated with the intraspinous injection of protoargol recommended this substance and said although its curative value had not been proved, that it can be injected in the subarachnoid space without harm. In 1916, Flexner and Amoss presented the results of their experiments with lysol and protoargol in the treatment of meningococcal infections in guinea pigs and monkeys. They found that these substances possess none of the properties which are essential for combating meningococcus infection. On the other hand, they showed that the use of such drugs might have a harmful effect when combined with serum treatment inasmuch as they prevent leucocytosis and inhibit the phagocytosis of the organism. Carbolic acid, flavine and eusol and many other antiseptics have likewise been recommended for intraspinous treatment. The consensus of opinion is that there is no favorable influence from the injection of other substances than antimeningococcus serum upon the course of the meningococcus meningitis.

As a result of their experiments regarding the antibactericidal properties of human serum MacKenzie and Martin in 1908 injected from 15 to 20 cc. of fresh human serum into the spinal canal of 16 patients with meningococcus meningitis. Ten of these patients recovered. Since then a relatively large number of cases have been reported in which either the patient's own serum or convalescent serum has been used intraspinously in the treatment. Both favorable and unfavorable results have been reported, but on the whole the use of human serum has not been followed with brilliant results. Fairly and Stewart as well as Kolmer and his collaborators have endeavored to reinforce the complement activity of antimeningococcus serum by the addition of human and of rabbit serum. In Fairly and Stewart's cases thus treated the mortality was about 30 per

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cent whereas in cases treated with serum alone the mortality was 50 per cent.

Much dissatisfaction with the results of serum treatment was expressed in England during the early months of the war and for a time the medical authorities were unable to decide how much benefit was derived from the intraspinous injection of antimeningitis serum and how much from the associated puncture. Indeed some authorities stated that in their opinion the old method of lumbar puncture and drainage without serum was the better form of treatment. As is well known, the explanation for the failure of serum was found when it was shown that the strains of meningococci causing the infection were in the majority of cases different from those used in preparing the antimeningococcic serum that was employed. As a result of this experience, however, numerous reports have been made regarding the beneficial effects of repeated lumbar puncture without serum administration. Olitsky in an epidemic in Southern China in 1918 had the opportunity of seeing cases which received no treatment and those in which lumbar puncture alone was performed. The mortality rate without treatment in 104 cases was 84.6 per cent, with repeated lumbar puncture in 346 cases it was 54.1 per cent. On the other hand, a number of authors have reported most unsatisfactory results from the use of repeated lumbar puncture without serum. This has been true not only during recent epidemics but in the treatment of the disease before serum treatment. In general, it would seem that by lumbar puncture alone the mortality from meningococcus meningitis can be reduced to a very slight degree, if at all.

Farmachidis has recently reported the successful employment of a normal salt solution in rinsing out the spinal cavity in a patient with meningococcus meningitis. He employed 360 cc. daily for twenty-five days. He would first withdraw 30 cc. of cerebrospinal fluid and then inject the same amount of salt solution. After a few minutes this was aspirated and allowed to flow out and 30 cc. were injected again. This was repeated 10 or 12 times at a sitting or until the cerebrospinal fluid finally came away clear. The cerebrospinal fluid became and remained clear after the twenty-third day. Aubertin and others have employed the same treatment. In my experience this method has not been attended with satisfactory results.

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VACCINES IN TREATMENT OF ACTIVE STAGES

Meningococcus vaccines as a curative measure were employed but little before the war. In the epidemics following 1915 they have been used by a large number of workers and there is a considerable literature on the subject. Inasmuch as they have been used for the most part in conjunction with other remedies such as serum and repeated lumbar puncture, their usefulness is rather difficult to determine. Sophian referred to their use in 1913 and stated that in certain cases they may be more efficacious than serum. Rolleston refers to 32 cases treated with autogenous vaccines together with serum or soamin in which there was a mortality of 25 per cent. Many of his cases were recovering but vaccines did not seem to alter the course of the severe infections. Worster-Drought and Kennedy report in detail several cases which apparently were favorably influenced by vaccine treatment in conjunction with serum therapy. Chalmers and O'Farrell report a case of recovery from severe and protracted meningitis with septicemia. They discontinued serum treatment and ascribe the cure to an autogenous vaccine. They advise the use of vaccine with serum therapy in all cases from the onset. Horden reports the case of a seven year old child to whom vaccine was given on the thirty-ninth day and after six days the temperature fell to normal. A relapse occurred two weeks later and vaccine again seemed to influence the disease as recovery took place. Crowe also speaks of vaccines as having a favorable influence on the temperature. Fairly and Stewart say that it is not uncommon to see a patient who has been having an irregular fever become afebrile shortly after vaccines are given. Out of 52 chronic cases they had a mortality of 32 per cent. Lewkowitz urges their early use and says that they tend to induce a general immunization which is a potent aid in the cure. Colebrook believes that they increase the antibactericidal content of the blood and so increase the value of the serum in its action against the meningococcus in the cerebrospinal fluid. Nearly all workers advise the use of an autogenous vaccine but when it cannot be obtained, a polyvalent vaccine containing the representative strains of meningococci may be substituted. The dosage advised has varied considerably. Worster-Drought and Kennedy inject 250,000,000 organisms subcutaneously at some time

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during the first three days and gradually increase the dose, 500,000,000 a dose, up to 2,500,000,000. The dose is modified for children. If there is a reaction to a particular dose, the same dose is repeated four days later. Walker-Hall gave a polyvalent vaccine in increasing doses from 25,000,000 to 500,000,000 every two days. Boidon gives from 200,000,000 to 750,000,000 every four days and MacLagan advises from 50,000,000 to 100,000,000 for the first dose. For the most part vaccines are recommended in the subacute or chronic stages of the infection when serum seems to become inefficient. In the acute cases but little benefit has been reported. No harmful effects with the exception of a temporary febrile reaction have been observed. Although the efficacy of vaccine therapy is not clear owing to its combination with other forms of treatment, until more information is available it would seem from so many favorable reports that in the subacute and chronic types of meningococcus infection this mode of treatment is worthy of trial.

As in other diseases for which there is a specific therapy certain general and symptomatic measures must be carried out in the treatment of meningococcus meningitis. The patient should be kept isolated in a quiet room or if in a hospital ward the patient should be separated from his fellow patients by a screen. The room or ward should be provided with an abundance of fresh air. Careful nursing is of the greatest importance particularly for delirious patients or those who are in coma. Much can be done to relieve the suffering of patients who are in a state of rigidity. Changing the position from time to time and supporting the head and knees with pillows will not only add to comfort but does much to prevent the development of hypostatic pneumonia and bed sores in those patients with a severe and prolonged form of the disease. The throat and nasal passages should be cleansed frequently with antiseptic washes and the eyes irrigated twice daily with boric acid solution. The diet is regulated according to the condition of the patient and every effort should be made to supply the patient with an adequate diet. A liquid diet is advisable during the acute stage. In unconscious and delirious patients feeding with a nasal tube or stomach tube must be employed. In patients with severe toxemia, water must be supplied freely. If there are evidences of desiccation, dryness of the skin and

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mouth, loss of tone in the skin or a great diminution in the amount of urine, salt or glucose solutions may be given intravenously, subcutaneously, by rectum or directly into the peritoneal cavity. I have seen several children during the acute stages of meningitis who were greatly improved after several intraperitoneal injections of normal saline. This method has been described by Blackfan and Maxcy.

It has been found experimentally by Weed and McKibben that the volume of the brain can be controlled by a change in the concentration of certain elements in the blood stream. They showed that the intravenous injection of hypertonic solutions of certain electrolytes and crystaloids causes a transient rise in the pressure of the spinal fluid which is followed by a marked fall which persists for a considerable period of time. With this idea in mind Hayden treated two patients by means of the intravenous injection of a 25 per cent glucose solution and thought that the favorable outcome was partly the result of a decrease in the intracranial pressure brought about by a change in the bulk of the brain. Hayden advises the intravenous injection of a 25 per cent glucose solution, as a routine measure every twelve hours from the onset of the disease until there is no longer any evidence of increased intracranial pressure. Rest is essential and should be secured by the use of morphine or other sedatives. Relief from headache, vomiting and other intracranial pressure symptoms are best relieved by repeated lumbar puncture. Symptoms of cardiac and respiratory failure should be combated with atropine adrenalin, camphorated oil and citrated caffeine in full doses administered intramuscularly.

HYDROCEPHALUS

Early in the history of meningococcus meningitis it was recognized that "the disease was distinguished by the slowness of its cure and that its duration might be a matter of several months." Unfortunately this is true and while recovery from the infection may take place, irremediable permanent damage may have occurred.

One of the most frequent of the sequelae is hydrocephalus. It has been customary to speak of the manifestations of increased intracranial pressure which are seen at the onset and throughout the course of the disease as symptoms of acute hydrocephalus. We know

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that these symptoms are largely due to the increased amount of cerebrospinal fluid which results partly from the stimulation of the choroid plexus and partly from the inflammatory process in the meninges which cannot be sufficiently rapidly removed by absorption even though this is but little interfered with in uncomplicated cases. There is a certain justification for speaking of acute hydrocephalus in some cases for the exudate may be so thick as partially or completely to obstruct for a time the foramina of exit from the ventricles. With time, especially when serum is used, this exudate frequently disintegrates and disappears and thus the channels of communication between the ventricles and the subarachnoid space are reestablished.

In patients never treated with serum chronic hydrocephalus is the most common of the sequelae and even in those actively treated by serum it results in a small but regrettable number of instances. This is especially the case with children. Hydrocephalus causes most of the striking symptoms seen in the subacute or chronic types of meningitis the rigidity of the limbs, the opisthotonos, the periodic vomiting, the peculiarity of the cry, the change in mentality and the enlargement of the head. The hydrocephalus is caused in the majority of instances by partial or complete blockage of the foramina Magendie and Luschka at the base of the brain or by obliteration of the cisternae (magna, interpeduncularis and pontis). The spinal subarachnoid space may also be more or less obliterated. In any event the free distribution of the cerebrospinal fluid throughout the cerebra and spinal subarachnoid spaces is prevented and its normal absorption is interfered with. Consequently there is an accumulation and retention of the cerebrospinal fluid within the ventricle. Anatomically, two types of hydrocephalus have been demonstrated: (*a*) the obstructive, and (*b*) the communicating. Obstructive hydrocephalus develops because the cerebrospinal fluid cannot pass from its place of origin in the cerebral and spinal subarachnoid space where absorption takes place. Communicating hydrocephalus—the channels of communication between the ventricles and the spinal subarachnoid spaces being patent to a greater or less degree—results because the cerebral subarachnoid space where the greater part of absorption takes place is partially or completely obliterated. In the majority of instances it is due to adhesions which obliterate the various cis-

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ternae or centers and obstruct the foramina. A combination of the two types of hydrocephalus may result if there is partial obstruction to the foramina and partial obliteration of the cisternae.

Attention must be directed to a hydrocephalus developing in meningitis by the onset of certain symptoms. The diagnosis is readily established when the condition is of long duration and the symptoms of increased intracranial pressure—headache, stupor, vomiting, enlargement of the head and changes in the eye grounds—are present. The early manifestations of hydrocephalus, however, are so closely interwoven with the symptoms of the meningitis itself that they are often difficult to recognize. Hydrocephalus should always be suspected with the persistence of symptoms of meningeal irritation (fever, hyperesthesia, irritability or drowsiness, rigidity of the muscles of the neck and extremities, hyperactive reflexes, tremors, etc.) or their reappearance after the symptoms of meningitis have subsided. Infants invariably have a tense and bulging fontanel and in older children and adults Macewen's sign is positive. It should be remembered that these symptoms cannot always be referred to the hydrocephalus alone.

Lumbar puncture yields the most information regarding the development of hydrocephalus, though it is not absolutely dependable. In hydrocephalus the cerebrospinal fluid is under greatly increased pressure and either an abnormal amount is readily obtained or it is obtained in small amount and with difficulty. A definite increase in the amount of cerebrospinal fluid of 50 cc. or more, withdrawn repeatedly when the other signs of the acute infection of the meninges have subsided, is significant of a communicating hydrocephalus. In obstructive hydrocephalus a large amount of cerebrospinal fluid may be recovered at the first lumbar puncture and then the quantity lessens so that only a few drops are obtained at successive punctures. Corroborative evidence of the presence of hydrocephalus may be shown by the results from puncture of the ventricle, as in such cases the cerebrospinal fluid in the ventricles is under increased pressure and an excessive amount can be withdrawn. During the acute stages of meningitis a small amount of fluid obtained by lumbar puncture suggests an obstructive hydrocephalus, for if the subarachnoid space has been entered and the fluid is not too thick to run through the

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needle, the prevention of a free flow of cerebrospinal fluid from the ventricles to the spinal subarachnoid space can hardly be caused by anything else than a thick exudate so situated as to obstruct the foramina of exit applied from the ventricles.

The differentiation between the two types of hydrocephalus by clinical signs alone, however, may be very difficult and for that reason I have employed in a number of cases the phenolsulphonephthalein tests used by Dandy and Blackfan in their study of chronic hydrocephalus. When phenolsulphonephthalein is injected into the ventricle in obstructive hydrocephalus, the dye does not appear in the cerebrospinal fluid obtained from the lumbar subarachnoid space within forty minutes, if at all. In patients who do not have hydrocephalus and in those with the communicating type of hydrocephalus, the phenolsulphonephthalein appears promptly (in from six to twelve minutes). When phenolsulphonephthalein is injected into the lumbar subarachnoid space in communicating hydrocephalus, absorption of the dye is greatly lessened. Less than 20 per cent is excreted in the urine within two hours, as compared to 35 or 60 per cent in normal persons. In obstructive hydrocephalus, when the cisternae and the meninges are not affected, absorption is as prompt as in normal individuals. In 17 cases of meningococcus meningitis communicating hydrocephalus developed in 8 patients and obstructive hydrocephalus in 9 patients. Ten of the 17 patients died. Two of the other 7 patients had an obstructive hydrocephalus and improvement followed promptly after the introduction of serum into the ventricles. The process in the 4 patients with communicating hydrocephalus became arrested after treatment. One patient with communicating hydrocephalus developed a chronic hydrocephalus in spite of the intensive intraventricular and intraspinous administration of serum.

Whenever in the course of meningitis fluid is obtained with difficulty or after temporary improvement there is a reappearance of the symptoms of meningeal irritation (hyperesthesia, vomiting, drowsiness, increased rigidity, etc.), or when in spite of active treatment improvement does not occur, an obstruction to the free passage of fluid from the ventricles and into the cisternae of the subarachnoid space is to be suspected. This not only leads to hydrocephalus but prevents

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the serum when injected below from reaching the inflammatory processes in the ventricles and over the surface of the brain. The injection of serum directly into the ventricles is then indicated.

INTRAVENTRICULAR INJECTION OF SERUM

The injection of serum directly into the ventricles was first employed by Cushing and Sladen. Since then it has been in rather general use. It is inadvisable to delay making use of this method. It should be resorted to in severe and complicated cases much more frequently than it has been in the past. Improvement may often and often does follow one or two injections of serum but repeated injection may be necessary. The dangers attending ventricular puncture are insignificant; in children it is oftentimes much easier than lumbar puncture. In infants the method of procedure is as follows: The patient should be wrapped in a blanket and placed in the recumbent posture on a table. The head must be firmly supported. An area corresponding to the anterior fontanelle having been shaved and the skin sterilized, the anterior fontanelle is outlined and an ordinary lumbar puncture needle with stylet is introduced just to one side of the mid-line to avoid the longitudinal sinus. The needle is pointed in a direction forward and slightly outward on a line with the optic foramen, and is pushed in to a depth of about $1\frac{1}{4}$ inches (3 cm.). When the ventricles are much dilated and the cerebral cortex thinned, the needle entering in almost any direction will usually find fluid. In older children and adults the method of trephining as devised by Keen or Kocher may be employed. It is always advisable to withdraw by aspiration large quantities of cerebrospinal fluid. Far larger amounts of serum can be introduced without danger into the ventricle than by the intraspinous route. It is preferable to enter each ventricle on alternate days but in the cases requiring trephine it has been our custom to inject through a single opening. Complete drainage of both ventricles can be accomplished easily by changing the position of the head during the process. Care should be observed when one opening is used that there is free communication between the ventricles. Cases have been reported in which the exudate has blocked the foramina of Munroe and under such circumstances the serum would not circulate freely within the ventricular

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cavities. Various surgical procedures having for their objective continuous drainage have been employed but such methods offer no improvement over the method of ventricular puncture, with serum administration during the period of acute symptoms.

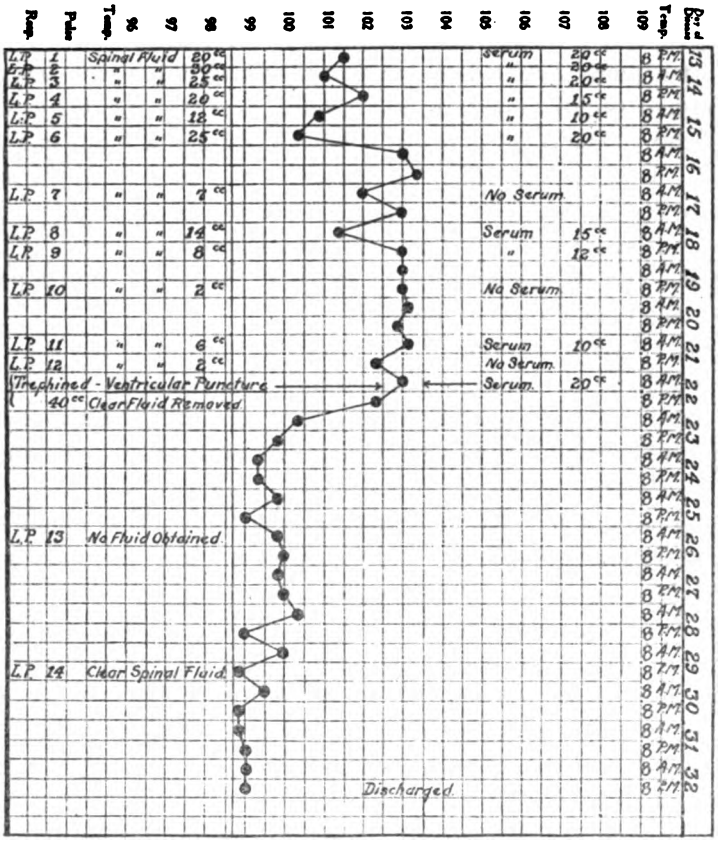
L.P. 1 Spinal Fluid 20 cc
L.P. 2 " " 30 cc
L.P. 3 " " 25 cc
L.P. 4 " " 20 cc
L.P. 5 " " 12 cc
L.P. 6 " " 25 cc
L.P. 7 " " 2 cc
L.P. 8 " " 14 cc
L.P. 9 " " 8 cc
L.P. 10 " " 2 cc
L.P. 11 " " 6 cc
L.P. 12 " " 2 cc
Trephined - Ventricular Puncture
40 cc Clear Fluid Removed
L.P. 13 No Fluid Obtained
L.P. 14 Clear Spinal Fluid
Serum 20 cc
" 20 cc
" 20 cc
" 15 cc
" 10 cc
" 20 cc
No Serum
Serum 15 cc
" 12 cc
No Serum
Serum 10 cc
No Serum
Serum 20 cc
Discharged

CHART VII.

SLIGHT IMPROVEMENT WITH INTRASPINOUS THERAPY BUT IMMEDIATE CURE WHEN COMBINED WITH INTRAVENTRICULAR TREATMENT

OTHER LOCATIONS RECOMMENDED FOR THE INJECTION OF SERUM

The introduction of fluid in other locations in order to overcome obstruction has been attempted by different clinicians. Chartier, Cantas, Ravaut and Krolunitsky and Netter have injected serum

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in the dorsal and cervical regions. Punctures of the subarachnoid space in these locations were followed in some of their patients by convulsions. A patient so treated by Cantas recovered. Cazamian treated three patients by the injection of serum through the orbito-sphenoidal route. One patient recovered. The technique of sphenoidal puncture is as follows: A pointed trocar and cannula is introduced at a point 2 mm. from the supraorbital notch, the trocar is then pushed slightly upwards and inward to reach the bony vault of the orbit. The pointed trocar is withdrawn and a blunt one substituted. By a little probing the most external portion of the sphenoidal fissure is reached. A fibrous membrane is pierced. The trocar, the inner end of which is in contact with the base, is then withdrawn and cerebrospinal fluid escapes. Serum is then injected through the cannula left in position.

Wegeforth and co-workers have used the space between the occiput and atlas to obtain cerebrospinal fluid from animals and believe that it may readily be used in man. They state that by this procedure specific therapy could be given more efficiently in early meningitis and indicate that it should prove of value in reaching the upper fluid reservoirs of the central nervous system when the spinal subarachnoid space is blocked. At the present time the method is the most satisfactory that has been devised when there is obstruction and when for any reason serum cannot be injected directly into the ventricles. Whether it has an advantage over the ventricular route remains to be determined.

In the chronic form of hydrocephalus after adhesions have taken place and when viable organisms cannot be demonstrated, the process cannot be further influenced by the injection of antimeningococcus serum. In the communicating type of hydrocephalus repeated lumbar puncture may be tried in the hope that the removal of large amounts of cerebrospinal fluid at regular intervals will retard the further development of the hydrocephalus until an equilibrium between the production of cerebrospinal fluid and its absorption is established. Although this does take place in a small percentage of cases, repeated lumbar puncture should only be tried temporarily, as permanent relief by more radical surgical methods cannot be expected if the hydrocephalus has reached an advanced degree. In obstructive

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hydrocephalus early surgical interference is indicated. Operative measures for the relief of chronic hydrocephalus heretofore have been uniformly unsuccessful. It is hoped that by the methods devised by Dandy successful results will be secured for the relief of this otherwise hopeless sequela of meningococcus meningitis.

OTHER COMPLICATIONS AND SEQUELAE OF MENINGITIS

To those who have had experience with meningitis before and after the introduction of serum treatment, it is very evident that by serum treatment the complications and serious sequelae have been greatly reduced. Statistics bear this out. Recovery in the great majority of cases treated is complete. Flexner states that formerly there were sequelae in about 20 or 25 per cent of the 25 per cent of patients that recovered from meningococcus meningitis. In the recent epidemics with serum treatment they have been reduced to about 6 per cent.

Worster-Drought and Kennedy have collected the more serious sequelae which have occurred in 120 patients from two months to one year after recovery. Their summary follows:

	cases
Strabismus	2
Blindness (One eye)	1
Monoplegia (Function restored 7 months after recovery)	1
Hemiplegia (Function restored 7½ months after recovery)	2
True neurasthenia	4
Deafness	2
Deafness partial	1

Of 94 patients in military service 11 were discharged because of the following sequelae:

	cases
Neurasthenia	5
Deafness	2
Strabismus	1
Blindness	1
Residual weakness of 1 foot after hemiplegia	1
Persistent pain in lumbar region on exertion	1

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According to Flexner's figures in the preserum period deafness was found in 12 to 33 per cent of the cases recovering. Among the serum treated cases it occurs in only 3.5 per cent. Deafness of central origin resulting from meningococcus meningitis is an early symptom and when it occurs it is almost always permanent. It is not influenced by treatment.

Eye complications are less frequent and take the form of a conjunctivitis, a severe uveitis, panophthalmitis and optic atrophy. Four to 6 per cent of the cases formerly developed eye complications. In Flexner's series the incidence was only 1 per cent. Uveitis may be and usually is followed by a panophthalmitis. As loss of vision is the usual sequel, the drastic method of the early intravitreous injection of serum has been advised. Netter reports two cases in which this was followed by improvement and the preservation of sight. Optic atrophy resulting from hydrocephalus is permanent and incurable.

Arthritis as a complication of meningococcus meningitis has been recognized for many years. Herrick and Parkhurst and Sainton have recently reported series of cases of arthritis which they have observed in recent epidemics. They found that arthritis not only might be associated with meningitis but it might be associated with meningococcaemia apart from a meningitis. A distinction has to be made between the arthritis resulting from meningococcus infection and that which occurs with serum sickness. Symptoms of arthritis depending upon an infection may occur at the onset of the disease or they may appear as late as the fifth or sixth day. The swelling may be great but there is always a striking disproportion between the amount of swelling and the other signs of inflammation, redness and pain, etc. Cure is usually spontaneous. The injection of serum directly into the joint in severe cases has been advised.

In the subacute and chronic stages of meningococcus meningitis, a secondary bronchopneumonia frequently occurs as a terminal event. Most frequently it is due to the pneumococcus, streptococcus or staphylococcus aureus. It is not unusual to recover the meningococcus from the sputum and from the lungs postmortem in such cases. That the meningococcus may produce a fatal pneumonia has also been recognized. Holm and Davison, as the result of their studies of pneu-

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monia in France found that the meningococci present in the lungs in cases of meningococcus pneumonia were essentially the same type of organisms as those present in the cerebrospinal fluid. They showed that the organism may produce either a lobular or a lobar pneumonia with or without a meningitis. Treatment with serum intravenously or with vaccines should be tried in such cases.

Other complications such as pericarditis, myocarditis, endocarditis, pyelitis, cystitis, paralyses, etc., are to be treated according to the usual methods.

In the convalescent period of meningococcus meningitis various symptoms may appear. These are paralyses, irritability, pain, weakness and stiffness of the back, mental impairment, neurasthenia, etc. There is often awkwardness in walking and even paralysis of the bladder and rectum have been reported. Much attention has been directed to these symptoms since the introduction of serum treatment. It has been considered by some authors that these symptoms are the direct result of the repeated lumbar punctures and the injection of antimeningococcus serum. Whether they are or whether they are sequels of the disease itself it is hard to determine. Some writers have maintained that lesions of the cauda equina are responsible for many of the symptoms. Worster-Drought and Kennedy carefully examined 120 patients who had recovered from meningitis for evidences of such lesions. The number of punctures which had been performed on the patients varied from four to thirty-five. In no case were there any areas of anesthesia corresponding to the distribution of the fourth and fifth sacral nerves. Worster-Drought and Kennedy believe that pain and weakness in the back are a sequel of the disease and are not dependent on the punctures and administration of serum. Fortunately the symptoms that have been described are relatively rare. They are more common with adults than with children. They may disappear early in convalescence or they may persist for weeks or months. Recovery is usually complete.

SERUM DISEASE

The manifestations of serum disease in general that follow the injection of antimeningococcus serum are much the same as those

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that follow the injection of any therapeutic sera made by immunizing horses. It was believed at one time that the manifestations were more frequent after the intraspinous injection than after the intramuscular or subcutaneous injection of serum but Rolleston and Kerr are of the opinion that this has not been proven. The incidence of serum sickness is influenced by the source of the serum as it is well known that serum from some horses is more apt to provoke serum sickness than that from others. The amount of serum injected may have some influence upon the incidence of serum sickness. Longcope and Rackemann believe that the smaller the amount of serum the less frequent and severe the reactions. Judging from clinical experience, however, there seems to be no constant relation between the incidence of serum disease and the amount of serum injected at one dose or the total amount used in the treatment of a patient. The symptoms usually appear from the 7th to the 10th day after the first dose of serum, although they may appear earlier or later than this. The commonest symptom to appear is an urticarial or erythematous rash and with its appearance there may be an initial rise in temperature. In many cases joints become red, swollen and tender and even an effusion into the joint may take place. There are muscular pains especially in the back. Edema of the face and tongue and of the penis and the scrotum may develop. Inasmuch as the meningeal symptoms are often intensified during serum sickness, care must be taken not to mistake the recrudescence of meningeal symptoms due to a serum disease for a recrudescence of the meningitis. When in doubt as to a differentiation between them, the safest procedure is to make a lumbar puncture and examine the cerebrospinal fluid for meningococci. In many of the patients the symptoms are so mild that treatment is not necessary. In the more severe reactions with itching of the skin, the local application of sodium bicarbonate solution, a 1 per cent menthol solution or calamine lotion often affords relief but sedatives sometimes are required for the itching and it is frequently necessary to give them for the pain which accompanies arthritis. The hypodermic administration of adrenalin in full doses often will cause the edema and urticaria rapidly to disappear.

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ANAPHYLAXIS

Although a primary injection of serum does not always sensitize an individual, symptoms of anaphylaxis do occur in about 75 per cent of the patients if they receive serum at such intervals that a week or more elapses between doses. The symptoms may be as mild as those occurring in serum sickness, or they be very severe and alarming. There may be an universal urticaria or a marked edema especially of the mouth, ears, eyes and larynx. The patient may become cyanosed with great respiratory distress. The temperature is often elevated. As a rule the symptoms gradually subside but marked prostration is apt to continue for several days. The severe reactions may occur after a short latent period of time or they may come on immediately (Goodall). Fatal results following the injection of serum are rare. Most of the cases reported have been in individuals who were hypersensitive to protein such as those who have suffered from asthma or in people with the habitus known as status thymico-lymphaticus. In such patients a death almost always occurs immediately following the first injection of serum.

A patient who is sensitive to foreign protein or who has shown symptoms of anaphylaxis at a preceding injection should always be desensitized before the reactivating therapeutic dose is administered. This may be done by diluting 5 cc. of serum with 50 cc. of normal saline solution and injecting intravenously small amounts (1 to 25 cc. of the dilution) slowly at intervals over a period of fifteen minutes. Fifteen minutes after the last injection the full dose may safely be administered. At any time during the administration of serum, if symptoms of anaphylaxis appear, the injection should be discontinued. The attempt may be repeated later after desensitization. The alarming symptoms are combated by epinephrin 1:1000 solution, 5 to 20 minims and atropin grains $\frac{1}{60}$ to $\frac{1}{120}$ injected intramuscularly or intravenously. Whenever serum is being administered these solutions should be ready for immediate use in case symptoms of anaphylaxis develop.

INFLUENCE OF SERUM THERAPY ON THE DISEASE

Statistics which show the effect of the serum treatment of meningitis in comparison with the results of preserum treatment are striking.

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Jochmann in 1906 had a death rate of 27 per cent as compared with 53 per cent in the untreated cases; Kolle and Wassermann in 1907 reported a mortality of 47.3 per cent in serum treated cases. Levy had a mortality of 16.2 per cent and 21.7 per cent in two epidemics and Flexner and Jobling reported a mortality of 25 per cent in 393 cases. When it is remembered that the average mortality of meningococcus meningitis untreated by serum was from 60 to 80 per cent whereas the average mortality for three years following serum therapy was 36 per cent, the benefits from the serum can readily be appreciated. The following table of statistics compiled by various observers illustrates the mortality rate before serum treatment compared with that following its use. These figures leave no doubt as to the effectiveness of this form of treatment.

AUTHOR	CASES TREATED WITH SERUM	SERUM USED	SERUM TREATED MORTALITY	CASES NOT TREATED WITH SERUM MORTALITY
Flexner.....	1300	Flexner's	30.9	70
Netter.....	100	Flexner's	28.0	49
Robb.....	300	Flexner's	30.0	72
Dopter.....	402	Dopter's	16.4	65
Levy.....	165	Kolle-Wassermann	18.4	52
Steiner.....	2280	Flexner's	37.0	77

So far as the benefits of serum treatment are shown, one need not look further than the figures which are given above.

The beneficial results of the serum are particularly apparent in the results obtained with small infants. Children under two years of age without serum almost always died and the mortality in those under a year was nearly 100 per cent. While meningitis is still most fatal in young children, a considerable number of infants may be saved, even some as young as three months of age. Seventy-eight patients under two years of age with meningococcus meningitis have been treated in this clinic and the mortality has been 52 per cent. Furthermore with serum treatment the number of complications and sequelae has been greatly lessened as has been pointed out.

The mortality even with serum therapy is likely to vary greatly in different epidemics and at different times in the same epidemic.

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Early in epidemics there are a larger number of fulminating cases than at the close and the virulence of the infection tends to subside and to be least in sporadic cases. For these reasons the mortality even with serum treatment is apt to be high at the beginning of the epidemics. The duration of the disease before treatment is begun has a great influence upon the mortality. This has been the experience of all observers as shown in the following chart:

Mortality per cent compared with day of beginning therapy

DAY	FLEXNER	NETTER	DOPTER	CHRISTMANOS	LEVY	FLACK
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Before 3.....	18	7	8	13	13	9
From 4 to 7.....	27	11	14	25	29	
After 7.....	36	23	24	47	28	50

Finally the factor which has the greatest influence on the mortality of meningococcus meningitis is the potency of the serum employed. During 1914 to 1915 when meningococcus meningitis appeared among the armed forces of Great Britain, the results of serum treatment were so unsatisfactory that a number of workers were inclined to believe that as much benefit was obtained from lumbar puncture alone as by the use of serum. Foster and Gaskell in their monograph on cerebrospinal fever not only advocate lumbar puncture as the only reliable therapeutic procedure but suggest that the injection of serum may even do harm. Many of the cases were not treated sufficiently early and the dosage of the serum and frequency with which it was administered varied within wide limits. It was then shown that the quality of the serum was of low standard and its potency practically nil owing to the fact that the strains of meningococci causing the infection were not used in the preparation of the serum. Later when a serum was employed which contained all the types of the organism criticism of the effectiveness of antimeningococcus serum ceased. In the first year of the war the mortality in serum treated cases was 61 per cent. In the following years when a properly prepared and standardized serum was used, it was about 27 per cent. This experience has demonstrated that the commercial manufacturer cannot be permitted to determine the method of preparation and choose his own standard of potency.

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REFERENCES

AMOSS, H. L., AND WOLLSTEIN, M.: Jour. Exper. Med., 1916, xxiii, 403.
AMOSS, H. L.: Jour. Amer. Med. Assn., 1917, lxix, 1137.
AMOSS, H. L., AND MARSH, PENELOPE: Jour. Exper. Med., xxviii, no. 6, 779.
ALBRECHT, H., AND GHON, A.: Wien Klin. Wchnschr., no. 41, 1902.
AUBERTIN: Gazzetta degli Ospedali e delle cliniche Milan, 40, 91, 988.
AMOSS, H. L., AND EBERSON, F.: Jour. Exper. Med., 1919, xxix, 6, 507.
AUSTRIAN, CHARLES: J. H. H. Bull., 1918, xxiv, 183.
BRIOT AND DOPTER: Compt. Rend. Soc. de biol., 1910, lxix, 174.
British Medical Research Report, Nat. Health Insurance, no. iii, 1917, p. 57.
BLOCK, J. H.: Jour. Amer. Med. Assn., 1914, lxiii, 2126.
BOVAIRD, D.: Arch. Int. Med., 1909, iii, 268.
BETTINCOURT AND FRANCIS: Ztschr. f. Hyg. 1904, xlvi, 463.
BAESLACK, F. W., ET AL.: Jour. Amer. Med. Assn., 1918, lxx, 684.
BRULE: Bull. et mem. Soc. med. d. hop. de Paris, 1918, xliii, 537.
BROWNING, C. K.: Brit. Jour. Surg., 1916, iv, 13.
BUIDON: Bull. et mem. soc. med. d. hop. de Paris, 1918, xliii, 317.
BLACKFAN, K. D.: Am. Jour. Dis. Child., xviii, 525, 1919.
BLOCH AND HERBERT: Arch. de med. et pharm. Paris, 1918, lxix, 697.
BLACKFAN AND MAXCY: Am. Jour. Dis. Child., January, 1918, xv, 19–28.
COMPTON, A.: Lancet, 1917, ii, 15.
COUNCILMAN, MALLORY AND WRIGHT: Report of State Board of Health, Massachusetts, Boston, 1898.
CHALMERS AND O'FARRELL: Trop. Med. and Hyg., London, 1915–1916.
CORNING: N. Y. Med. Jour. 1885, xlii, 483.
CROHN, B.: Jour. Amer. Med. Assn., 1911, lvi.
CARTER: Epidemic Cerebro-spinal Meningitis, Sophian, p. 211.
CROWE, WARREN: Proc. Roy. Soc. 1916, November 9.
COLEBROOK AND TANNER: Med. Research Committee report on cerebrospinal fever, 1916, London.
CROWE, S. J.: J. H. H. Bull., 1909, xx, 13.
CUSHING, H., AND SLADEN, F.: Jour. Exper. Med., 1908, x, 548.
CHARTIER, M.: Revue de Med., 1914, 8, xxxiv, 585.
CAZAMIAN, P.: Bull. et mem. soc. med. d. hop. de Paris, 1916, xxxii, 361.
DOPTER, C.: Compt. rend. soc. biol., 1909, lxvii, 74.
DOPTER, C.: Compt. rend. soc. biol., 1909, lxvi, 772.
DUVAL: Jour. Med. Research, 1908, xix, 258.
DOCHEZ, A. R.: Jour. Exper. Med., 1909, xi, 718.
DANDY, W. E., AND BLACKFAN, K. D.: Jour. Am. Dis. Child., 1914, viii, 406.
DANDY, W. E.: Annals of surgery, December, 1918.
ELSER AND HUNTOON: Jour. Med. Research, 1909, 15.
FLEXNER, SIMON: Jour. Amer. Med. Assn., 1906, xlvii, 460.
FLEXNER, S.: Jour. Exper. Med., 1907, ix, 105.
FLEXNER, S.: Jour. Exper. Med., 1907, ix, 168.
FLEXNER, S., AND JOBLING, J. W.: Jour. Exper. Med., 1908, x, 141.
FLEXNER, SIMON, AND JOBLING, J. W.: Jour. Exper. Med., 1908, x, 690.
FLEXNER, SIMON: The Edinburgh Medical Journal, May, 1912.

Digitized by Google

FLEXNER, S.: Jour. Amer. Med. Assn., 1913, lx, 6, 1937.
FLEXNER, S., AND AMOSS, H. L.: Jour. Exper. Med., 1916, xxiii, 683.
FLEXNER, SIMON: New York, 1917, Rock. Ins. for Med. Research.
FOSTER AND GASKELL: Cerebrospinal fever, Cambridge, 1916.
FAIRLEY, N. A., AND STEWART, C. A.: Australian Service Publ., no. 9, Melbourne, 1916.
FARMACHIDIS, C. B.: Gazzetta degli Ospedali e delle cliniche, Milan, 40, 91, 988.
GORDON, M. H.: G. B. National Health Ins. Med. Res. Com. Spec. Rep. Series, no. iii, 1917, 10.
GORDON, M. H.: British Med. Jour., 1918, i, 110.
GORDON AND HINE: Med. Research Com., January 28, 1919.
GREENWOOD, M.: Proc. Roy. Soc. Med., 1916–1917.
GATES, F. L.: Jour. Exper. Med., xxviii, no. 4, p. 449.
GERSTENBERG AND HEIN: Quoted from WORSTER-DROUGHT AND KENNEDY.
GOLDEN, W. E.: U. S. Naval Med. Bull., 1918, xii, 24.
GOODALL, E. W.: Lancet, 1918, i, 323-361.
HIRSCH, AUGUST: Handbook of Geographic and Historical pathology, 1886, vol. iii, p. 546.
HITCHENS, A. P., AND ROBINSON, H. H.: Jour. Immun., 1916, i, 345.
HINE, T. Q. M.: English report, p. 99.
HOHN: Klin. Jahrbuch, 1909, xx, 357.
HORDER, T. J.: The practitioner, 1916, 96, p. ii. Cerebrospinal Fever, 1915.
HERRICK, W. W.: Jour. Amer. Med. Assn., 1918, lxx, 227.
HERRICK, W. W.: Jour. Amer. Med. Assn., 1918, lxi, 612.
HERRICK AND PARKHURST: Amer. Jour. Med. Sc., 1919, clviii, 4, 473.
HALL, W.: Bull. 91, Hyg. Lab. U. S. P. H., 1914.
HOLM AND DAVISON: J. H. H. Bull., 1919, xxx, 345.
HADEN, R. L.: Jour. Amer. Med. Assn., lxxiii, 983, 1919.
JOCHMANN, G.: Deutsch. Med. Wchnschr. No. 20, 1906, 788.
JOCHMANN, G.: Deutsch. Med. Wchnschr., 1911, xxxvii, 1733.
JOBLING, J. W.: Jour. Exper. Med., 1909, xi, 614.
JAEGER: Die Epidemische Meningitis, etc., Berlin, 1901, 196.
KOLLE AND WASSERMANN: Deutsch. Med. Wchnschr., 1906, xxxii, 609.
KRUMBEIN AND SHATILOFF, P.: Deutsch. Med. Wchnschr., 1908, xxiv, 1002.
KRAUS, R., AND DORR, R.: Wien. Klin. Wchnschr., 1908, xxi, 12.
KIEFER, F.: Berlin Klin. Wchnschr. xxxii, 1896.
KROENIG, QUINCKE AND OTHERS: Quoted by HEDMAN AND FELDSTEIN, p. 105.
KLUGGE: Klin. Jahrb., 1906, xv, 353.
KRAMER, S. P.: Jour. Amer. Med. Assn. May 3, 1913, xvi, 1348.
KERR, CLAUDE: The Lancet, 1917, ii, 822.
LEVY: Serum behandlung der epidemisch Oenickstarre, Jena, 1911.
LUSK: Annals Surgery, 1911, liv, 449.
LOCH AND HERBERT: Quoted by DOPTER, Lancet, June 21, 1919.
LEWKOWICZ, K.: Arch. de med. des enfants, Paris, 22, no. 12, 617.
LONGCOPE AND RACKEMANN: Jour. Exper. Med., 1918, xxvii, 341.
Medical Res. Com. Reports on bacteriological studies in cerebrospinal fever during epidemic 1915, London, 1916.
MAYER, WALDMAN, FÜRST AND GRÜBER: München. med. Wchnschr., lvii, 1910.
MCLAGAN, P. W.: Edinburgh Med. Jour., 1918, xx, 236.

Digitized by Google

MENJ AND GOVARD: Bull. Medicale Paris, 33, no. 52, 691.
MANGES, M.: Med. News, 1904, lxxxiv, 913.
MCKENZIE AND STEWART: Jour. Path. and Bacteriol., 1908, xii, 539.
NICOLLE, M., DEBAINS, E., JOUAN, C.: Ann. de l'Inst. Pasteur, 1918, xxxii, 150.
NETTER, A.: Arch. de Med. d. enfants 22, no. 2, February, 1918, p. 72.
NEUMANN, J.: Therap. Monatsh., Berlin, 33, 10, 369.
NETTER: Bull. de l'acad. de med. Paris, 1916, lxxv, 322.
NETTER: Rev. de med. 35, 133, 1917.
NOBECOURT AND PARAF: Arch. de Med. des enfants, Paris.
NETTER: Compt. rend. Soc. de Biol., 1915, 68–90.
NETTER AND SALAMIER: Bull. et mem. soc. med. des hop. de Paris, 1917, 3, xii, 299.
OLITSKY, P. K.: Arch. Int. Med., 1918, xxiii, 380.
PARKES, W. H.: Brit. Med. Jour., 1917, i, 262.
QUINCKE: Berlin Klin. Wchnschr., 1891, xxviii, 929.
ROLLESTON, SIR HUMPHREY: Lumelian Lectures, Lancet, 1919, i, 645.
ROLLESTON, SIR HUMPHREY: The Practitioner, 1916, 96, 13.
RIBIERRE, P.: Ann. de med., December, 1919, vi, 341.
RAVAUT, PL. AND KROLUNITSKY, G.: Bull. et mem. soc. med. d'hop. de Paris, 1915, xxxix, 618.
STILLE, ALFRED: Epidemic Meningitis or Cerebrospinal Meningitis, Lindsay and Blakiston, 1867.
STRONG: Diss. on the disease termed Petechial or spotted fever, Hartford, 1910.
SINGELSHEIM AND LEUCHS: Klin. Yahrb., 1906, xv, 489.
SOPHIAN, A.: Epidemic Cerebrospinal Meningitis, Mosby Company, St. Louis, 1913.
SOPHIAN, A. AND BLOCK, J.: Jour. Amer. Med. Assn., 1912, lix, 527.
SHIROORE, JR., AND ROSS, P. H.: Trans. Soc. Trop. Med. and Hyg., 1913, 83.
SEAGER, H. W.: Lancet, 1902, ii, 1188.
SAINTON, PAUL: Lancet, 1919, i, 1080.
TREADGOLD: Jour. R. A. M. C., 1916, July.
VIEUSSEUX, M.: Jour. de med., de chir. et de pharmacie, Paris, December, 1905.
WEICHSELBAUM, A.: Fortschritte der Medicin, V. Jahrgang, 1887.
WOLLSTEIN, M.: Jour. Exper. Med., 1914, xx, 201.
WASSERMANN: Deutsch. Med. Wchnschr., 1907, xxxiii, 1585.
WHITMORE, E. R., FENNEL, E. A., AND PETERSON, W. F.: Jour. Amer. Med. Assn., 1918, lxx, 427.
WYNTER: Lancet, 1891, ii, 981.
WORSTER-DROUGHT AND KENNEDY, A. M.: Lancet, 1917, i, 803.
WALKER, THOMAS: Quoted by WORSTER-DROUGHT AND KENNEDY.
WOLF, C.: Deutsch. med. Wchnschr., 1915, xli, 1486.
WEGEFORTH, P., AYER, J. B., ESSICK, C. R.: Amer. Jour. Med. Sc., 1919, clviii, 183.
WEGEFORTH, P., AND LATHAM, J. R.: Amer. Jour. Med. Sc., 1919, clviii, 183.
WEED, S. H., WEGEFORTH, P., AYER, J. B. AND FULTON, L. D.: Jour. Amer. Med. Assn., 1919, lxxii, 1920.
WEED, L. H., AND MCKIBBEN, P. S.: Amer. Jour. Physiol., 1919, xlviii, 512.

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THE ETIOLOGY AND EPIDEMIOLOGY OF INFLUENZA

HANS ZINSSER

New York

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INTRODUCTION

The etiological and epidemiological problems of no disease can be intelligently discussed until we can precede discussion with a clear cut definition of the disease itself. In infectious diseases like smallpox, scarlet fever, measles, diphtheria, and pneumonia, investigation is sure to deal with a material which is amenable to reliable selection on clinical grounds. In the case of influenza it is the difficulty of sharply defining the disease, which has been, and still is, at the bottom of the confusion prevailing in research. Whenever widespread epidemics

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of so-called "catarrhal fever" have swept over large sections of the world, the epidemic characteristics in themselves, as well as a certain regularity of onset, sequence and similarity of course, have sufficiently indicated the basic identity of the cases. It has been clearly recognized, however, that except at the very beginnings of every epidemic, clinical manifestations have been dominated by the complications, rather than by the original infection. And these complications, in their localizations, pathology and bacteriology have been subject to wide variations. For these reasons the diagnosis of influenza made upon isolated cases of respiratory infection at times when no epidemic prevailed, has been admittedly more a clinical surmise than a scientifically formulated conclusion. This has been clear to well trained physicians for many years, and the term "influenza" has been used by them during interepidemic periods as a term of clinical convenience, to characterize conditions ranging in seriousness from severe coryza, with systemic symptoms, to fatal lobular pneumonia. It may well be that many of these cases have had a specific influenzal basis, and represent the smouldering embers from which the flames of new epidemics are lighted, but there is no way at the present time of being sure of this in individual cases.

It would be a relatively simple matter if we could base the diagnosis of true influenza upon the isolation of Pfeiffer bacilli, just as we determine the diagnosis of diphtheria by the isolation of the Klebbs-Loeffler bacillus. But for reasons which will become clear presently, this cannot be done. For, even through the Pfeiffer bacillus should eventually prove to be the specific etiological factor in influenza, it is still so frequent as a complicating agent in other respiratory infections, or perhaps as a symbiant in the upper air passages of normal individuals, that its mere presence in the secretions of a catarrhally inflamed mucosa, does not characterize the infection etiologically.

The relationship of this bacillus to the disease presents a problem of great complexity and of many uncertainties which will be discussed more extensively below. Before we can proceed to this, however, it will be necessary to specify more precisely just what we believe should be the proper characterization of uncomplicated influenza in a clinical sense. For unless this is clear it will be impossible to determine

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whether bacteriological or other etiological investigations have dealt with the disease itself or with one or another of the manifold complications.

HISTORICAL RÉSUMÉ

In the older works many accurate descriptions of uncomplicated influenza are available. Huxham writing of the epidemic which occurred in Plymouth in the first half of the eighteenth century, describes the disease as one of very sudden onset, chilliness and fever, usually lasting about four days, and rarely ending fatally. He mentions catarrhal inflammations of the nose and throat, and the frequent occurrence later in the disease, of a cough, but lays stress not upon these catarrhal symptoms, but rather upon the suddenness of onset, the fever, the short duration and the low mortality. Arbuthnot in 1732 speaks of a remarkable uniformity of symptoms, "a small rigor or chilliness, succeeded with fever of a duration seldom above three days." He says, "this disease was not in itself mortal, but it swept away a great many of poor, old and consumptive people." Thompson in his Annals of Influenza (London, 1852) summarizes the clinical manifestations by laying stress upon the sudden feverish onset, chilliness, and pains in the neck, back and loins, suffusion of the eyes; coryza and bronchitis are mentioned as later developments. Most of these writers, more especially Thompson, recognized the inflammations of the bronchi, pleura, and lungs as probable complications frequently present, but not as uniformly characteristic as the fever, pains, and the prostration which was often extreme without sufficient apparent reason in any discoverable lesions. It is interesting to note that these early writers described an intestinal form. Thompson speaks of it as follows: "When the lungs are not materially affected, the force of the morbid influence is in some instances directed to the bowels, producing pain and tenderness of the abdomen, and diarrhea, with mucous or dysenteric evacuations."

Leichtenstern described "typical influenza" as follows (we translate literally):

> Typical influenza consists in a sudden fever which is initiated by a chill or frequent chilly sensations, and lasts from one to several days, is associated with severe headache, especially in the frontal regions, vertigo, pain in the

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back and legs, disproportionately severe prostration, and loss of appetite. After ten to twelve hours perspiration ensues, and in twenty-four to forty-eight hours the fever has usually subsided in many of the patients, leaving them with great weakness and with pains in the muscles and joints which disappear within a few days.

In almost all of the patients in whom the onset is violent there is an immediately apparent diminution of urine. Many of the sick may not void more than 200 to 300 cc. of urine in twenty-four to thirty-six hours, and with this there is often constipation. Many may show an enlargement of the spleen.

By the third or fourth day as the patients recover, the constipation is relieved, the urine becomes more plentiful, the albumin disappears, and the splenic enlargement recedes.

This is the classical picture of influenza as Leichtenstern sets it down in the summarizing paragraphs at the beginning of his clinical chapter. He adds that: "symptoms of catarrhal inflammations of the respiratory passages and especially of the nasopharynx often supervene upon the manifestations described above, an occurrence which is perfectly natural in view of the localization of the influenza bacilli." Although, therefore, he does not make the direct statement, he implies that he considers the catarrhal inflammations as probably incidental.

It is a singular fact that, in spite of these and other accurate descriptions of uncomplicated influenza, published since the time of Sydenham, the disease has usually escaped general recognition in epidemics until complications have become frequent.

Thus, Heyfelder, who observed the beginnings of the 1889 epidemic in Russia and the East writes of "Sibirisches Fieber," which was at first looked upon as malaria owing to the apparently complete absence of the complicating lesions habitually associated in our minds with influenza. Of particular interest is his statement: "Auch fehlten bei den meisten die Katarrhalischen Affektionen der Respirations-Organen." When the disease appeared in Petrograd, in November, Heyfelder found that it corresponded accurately to the descriptions of an epidemic of "Dengue fever" which was said to have been prevalent in Constantinople during the preceding September.

The recent pandemic furnishes many similar examples of early confusion. When the disease first appeared at Camp Oglethorpe,

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Georgia, in March 1918, its precise nature was long undetermined though its similarity to influenza was recognized. Vaughan and Palmer writing of this outbreak say; "The identity of the disease has not been positively determined after nearly a month of observation;" and again they speak of it "as a disease with a strong resemblance to influenza." In Italy Sampietro suggested Sandfly fever, a thought which seems to have occurred to a number of British writers, and which led us, as well, to make a brief study of prevailing insects upon our first contact with the epidemic at Chaumont in May, 1918. Wherever the disease was first seen during the spring and summer of 1918 it was characterized by explosive suddenness of onset, and an enormous morbidity in individual groups within a few days; but it was mild in nature, with little or no mortality, rare complications and so few of the catarrhal symptoms usually associated with clinical conceptions of influenza that those that did occur were not always regarded as characteristic manifestations of the "new disease."

Many of the earlier reports received in the spring of 1918, therefore, were unanimous in agreement with the typical description of Leichtenstern. These made later in the year began progressively to emphasize the greater frequency of mild or severe inflammatory processes in the upper air passages. Fortunately placed observers could follow with considerable clearness the gradual transformation of the clinical types encountered in successive outbreaks, from the mild "three-day fever" of early spring to the grave respiratory illness of autumn. But there was still in the minds of a considerable number of people some question as to the basic identity of the early mild cases, and the severe epidemic bronchopneumonias of October and November.

CLINICAL COURSE OF INFLUENZA

It will be useful to discuss briefly the early cases as we saw them during the Chaumont epidemic, not because the observations made there add much that is new from a clinical point of view, but because they will remove any possible ambiguity concerning our conception of influenza in its pure uncomplicated form.

As far as we can judge, the little outbreak at headquarters was typical of the first advent of epidemic influenza in many places. The population of the town, at the time, consisted of a large office per-

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sonnel attached to the military administration, scattered as to billets and places of work; of military units living in barracks and eating at common masses; and of the townspeople. The epidemic descended upon individual military units with the suddenness of a storm, striking a considerable percentage of the men, perhaps most of the susceptible material, within less than a week, and ending almost as abruptly, with only a few isolated cases trailing behind. Among the more scattered office workers and among the townspeople it was disseminated more gradually and trailed along for a longer period.

These early cases were clinically so uniform that a diagnosis could be made from the history alone. The onset was almost uniformly abrupt. Typical cases would become ill suddenly during the night or at a given hour in the day. A patient who had been perfectly well on going to bed, would suddenly awake with a severe headache, chilliness, malaise and fever. Others would arise feeling perfectly well in the morning, and at some time during the day would become aware of headache and pains in the somatic muscles. Occasionally there was nausea. A few of the patients could state the exact hour at which they were taken ill. One of them became suddenly ill at the moment at which he was stepping into line for inspection. Another was taken ill while standing guard, and again another while being shaved. There were of course some cases in which the onset was more gradual, but our personal impression is that the sudden onset was the characteristic one, the more gradual one, the less usual or modified.

The typical course of these cases may be exemplified by that of J. T. W., a draftsman attached to the 29th Engineers. He was perfectly well until May 20, working regularly, his bowels and appetite normal, considering himself healthy. On May 21, at 4:30 a.m. he awoke with a severe headache. He arose, forced himself to eat breakfast and tried to go to work. He began to feel feverish and chilly. At the same time his headache became worse, with pains in the back, and burning in the eye balls. At 2 p.m. he reported sick, and was taken to the hospital with a temperature of 102.8°. At midnight his temperature dropped to 101.6°, and came down to normal by noon of May 22. As he recovered he developed a slight sore

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throat, great soreness of the legs and a very slight cough. He recovered completely within a few days.

These cases with a few exceptions developed no rashes. One or two of them had blotchy red eruptions which we felt incompetent to characterize dermatologically. The leucocyte counts ranged from 5000 to 9000. A very few went above this. Sometimes there was a relative increase of lymphocytes, but this was by no means regular. The few spinal fluids that were examined were normal. As to en-

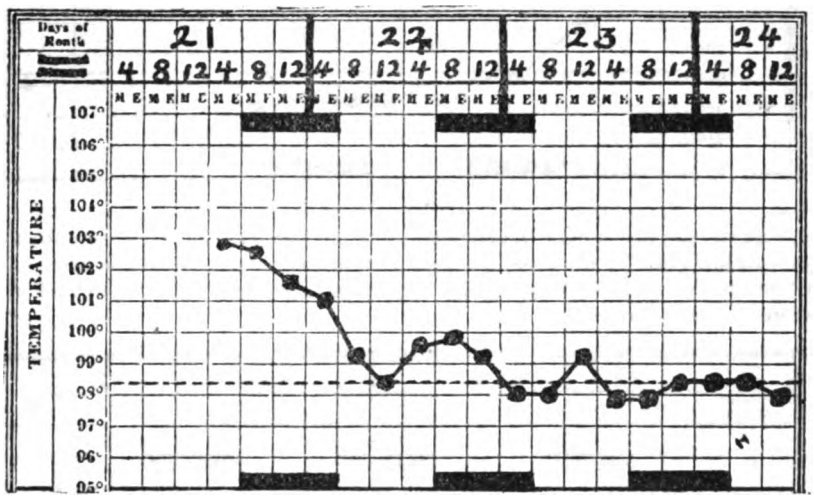

FIG. 1. J. T. W. COMPANY H., 29TH ENGINEERS[1]

Draughtsman. Perfectly well Monday, May 20. Woke up Tuesday, 4:30 a.m. with violent headache. Got up and ate a little breakfast and went to work, then began to feel feverish and chilly. Pain in back and headache and pain in eyes (burning), slight cough and pain in legs. Reported sick 2:00 p.m. Since arrival in hospital cough worse and slight sore throat.

largement of the spleen, we can say nothing definitely. Although we looked for spleens and failed to find enlargements, we are not willing, in view of our limited clinical habits, to say that they could not have been felt by more experienced men.

[1] These charts are taken from the report of Major Hans Zinsser, to the Chief Surgeon, A. E. F., May 31, 1918. Blocked spaces indicate night periods in this and following charts.

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We add a few typical charts.

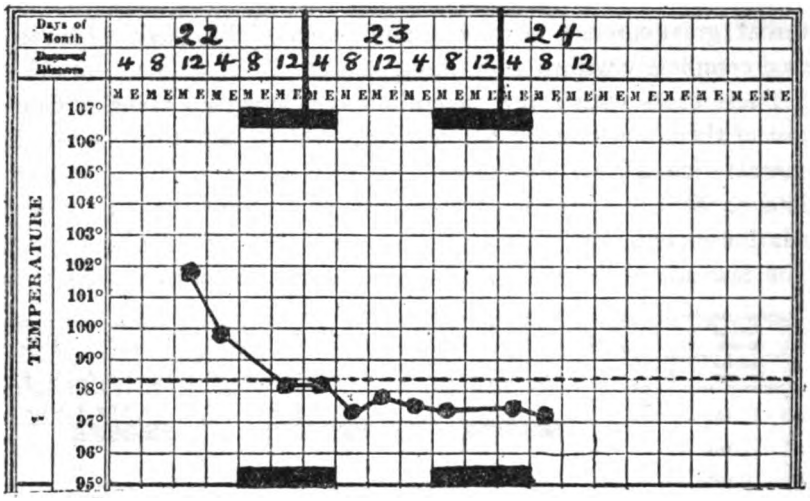

FIG. 2. H. W. COMPANY H., 29TH ENGINEERS

Slept in bunk next to W. Draughtsman, same office as W. Got sick on day after W. On Tuesday, May 21, afternoon, headache, pain in bones, fever, burning in eyes. Did not report sick until Wednesday, May 22. Slight sore throat. Felt better all over before he came to hospital.

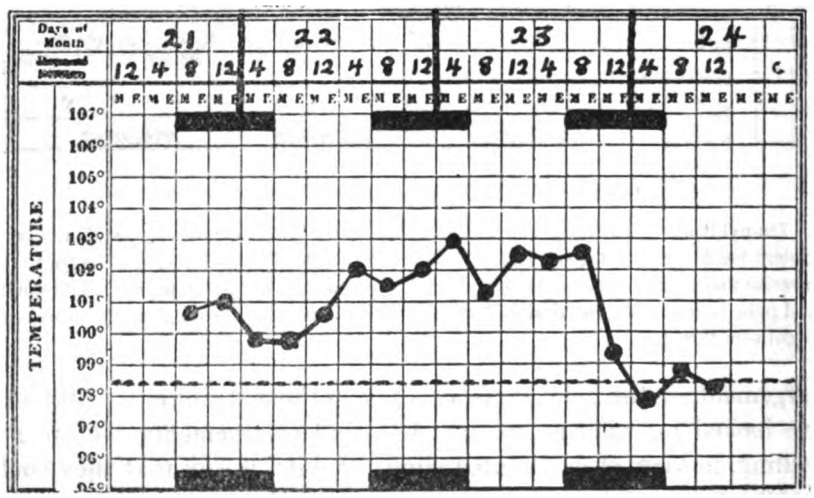

FIG. 3. S. L. COMPANY C., HQ. BN.

Was living with Company D when taken sick. Company Clerk. No one near him sick in same way. Messed with Company D. Felt well Monday, May 20. Tuesday, a.m. felt well until after breakfast, then headache. In afternoon went to dispensary and was sent to hospital. Very slight cough since arrival in hospital. Throat not sore now, and no pains. Is feeling well.

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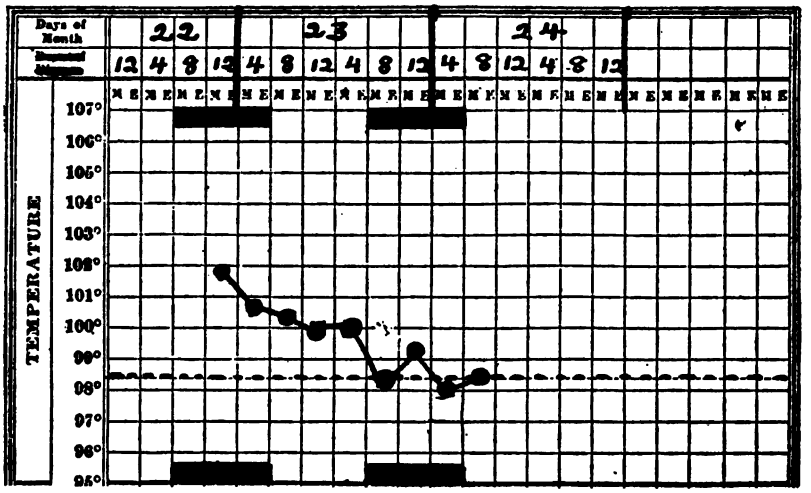

FIG. 4. C. S. COMPANY H., 29TH ENGINEERS

Orderly. Slept 4 bunks from F., sick in hospital now. Began to feel sick while at drill on Wednesday, a.m., May 22. Dizziness, stiffness in muscles, no sore throat. No other symptoms, went to dispensary because he felt feverish. Slight cough since arrival in hospital. Feeling well now.

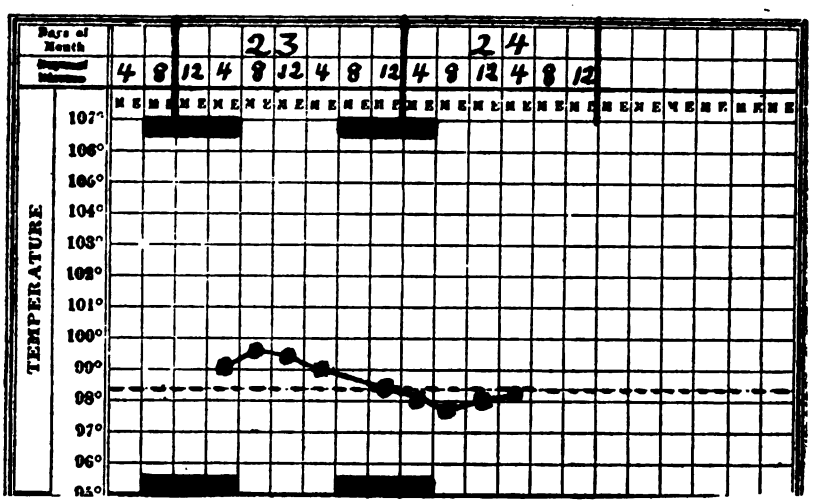

FIG. 5. M. MARINES

Slept in tent with one man, C., who had just come back from hospital. C. returned Monday, May 20. M. began to feel sick Wednesday, May 22, at night. Dizziness and headache, weakness, pain in back and legs. No nausea, nothing referable to intestines.

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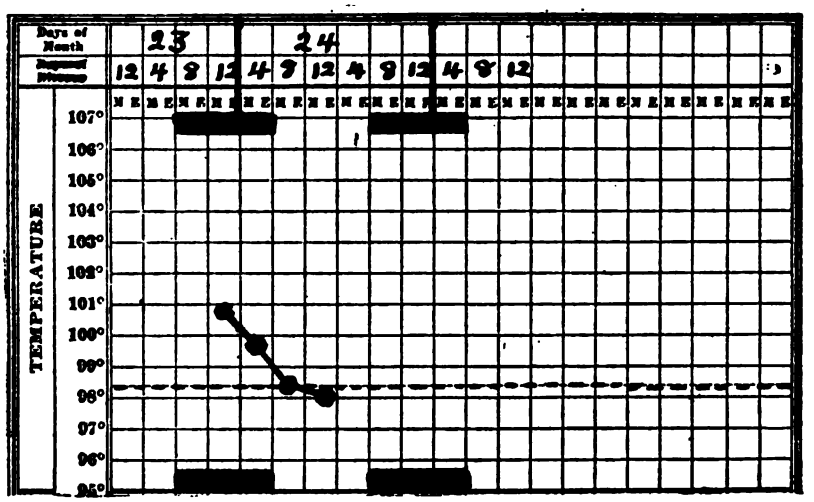

FIG. 6. R. S., A. M. T., COMPANY 304

Cook. Worked all day Wednesday. Began to feel sick about 4:00 p. m. Headache after supper, nausea. Not very sick, sent to hospital by attendant at dispensary.

Soon after this we observed the disease in a division, the 42nd, then holding a part of the line in front of Baccarat. Here it had already developed a somewhat different nature, due, we believe, to the fact that the men of this division were not, as were those at Chaumont, living in a rest area, but were actively engaged in military operations, working, sleeping, and eating under conditions that involved greater fatigue, less protection against weather, and greater crowding in sleeping quarters. The Baccarat cases were much more frequently catarrhal; sore throats, coughs and more serious respiratory complications were more common. However, they were usually coupled unmistakably with an underlying typical influenzal attack, sudden onset, pains and short lived fever. Moreover, there were a great many of the entirely uncomplicated cases interspersed with the others.

Still later, in September, October and November, respiratory complications were so frequent and severe, came on so early in the disease, and the pneumonia mortality became so high that the fundamental identity of these later cases with the early three-day fever might easily have been lost sight of by observers who had not followed the gradual transformation.

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In consideration of these facts, it is apparent that etiological or other investigations can throw no light upon the problems of influenza unless they are carried out with a clear understanding of the differentiation between the complications and the basic disease.

The serious respiratory infections of the bronchi and lungs we can set down with reasonable certainty as complications due, certainly in the overwhelming majority of cases, to secondary bacterial invaders. It is a matter of considerable difficulty, however, to know exactly where the basic disease stops and the complications begin; and whether we must regard the mild sore throat and conjunctival infection which so often accompany the simple cases as a part of this basic clinical picture, or as the simplest variety of complication. This is much more than an academic question, since, as we shall see, the bacteriological analyses of such lesions have played an important rôle in etiological investigations.

ETIOLOGY OF INFLUENZA

Former epidemics

The significance of sharp clinical definitions for etiological research in influenza is obvious. The simple form of the uncomplicated disease is common only during the early stages of epidemics. After this, most of the cases may perhaps begin with this basic condition, but are very rapidly complicated by more or less serious inflammatory involvement of the respiratory passages. Some of the milder and perhaps some of the more serious and even fatal of these complications may be due to the infectious agent which causes the original disease; but a great many of them we know are caused by secondary invaders, and for this reason bacteriological analyses made from the secretions and the lesions of the respiratory passages in such cases must be interpreted with constant realization of the possibility that we are dealing with secondary invaders and not with the primary infectious agent. This has been the difficulty in etiological influenza research, and in the light of this confusing state of affairs, no results are of great value unless combined with a correspondingly careful clinical analysis of the cases from which the material has been taken.

When the pandemic of 1889 was beginning to trail into its last stages

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there seemed to be little doubt in the minds of investigators concerning the etiological significance of the Pfeiffer bacillus. At the present time, with the experiences of another outbreak behind us, we are less certain of this relationship than we were before.

It will be well to state, at the beginning, that we do not believe that final conclusions concerning the etiology of influenza are warranted at the present time. The problem has been a singularly difficult one, largely owing to the indefinite clinical conceptions of the disease alluded to above. For these reasons one cannot do justice to the etiological problem without discussing at some length the more important investigations which have dealt with this subject during the two last epidemics and in the interepidemic period.

After 1889 many etiological "suggestions" (we had best term them) were made, prior to the publication of Pfeiffer's observations. Klebs reported that he had found protozoa in influenza lesions, a claim which finds an interesting parallel in the recent reports of Binder and Prell who have described minute coccoid bodies in the tissue spaces around blood vessels in influenza lungs, and the subsequent development in cultures from such material of small organisms which they regard as "chlamydozoa." Comment on such findings is unprofitable at the present time. We can merely "file" them in our minds for reference and, perhaps, future explanation. The past has been too rich in misleading interpretations of so-called "chlamydozoan" cell inclusions (variola, trachoma, etc.) to encourage optimism concerning such claims.

As in the recent outbreak the preceding one was the occasion for etiological proposals involving the Gram-positive cocci, more particularly the pneumococcus and streptococcus groups. However, it is perfectly natural that bacteria which habitually inhabit the upper respiratory passages, and are potentially pathogenic, should be isolated with great frequency from influenza cases, and, therefore, incite suspicion of etiological importance; but none of these can be seriously considered. Indeed, in the light of our present differentiation between the basic disease and the complications, the streptococci and pneumococci may be regarded as practically eliminated as primary causations of influenza. The same is true to an even greater degree of organisms like micrococcus catarrhalis, meningococcus, para-

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typhoid bacilli, and many other bacteria which have been isolated from time to time as characteristic findings in small groups of cases occurring in special localities. Some of these investigations will be briefly dealt with in a later paragraph.

We believe, indeed, that we are justified in basing our discussion of etiology upon the assumption that none of the bacteria so far described can be seriously considered in this connection except the group of haemophile organisms of which we speak as "Pfeiffer bacilli." If influenza is truly a disease of bacterial causation these precede all other bacteria in etiological likelihood.

Pfeiffer published his first announcement in 1892, reporting that he had found the organisms, which are now familiar to us as the typical influenza bacillus, in the sputum of patients, but had failed to find them in normal controls. In a subsequent article in the Zeitschrift für Hygiene (13, 1892) he brought together the large material of his researches, the results of which may be stated briefly as follows.

The organisms were present in large numbers in the sputa of early cases and, at this early stage, were largely extracellular. Later, most of the sputum organisms became intracellular and, in the milder cases, gradually disappeared. In cases with pulmonary complications which came to autopsy, if the bacterial contents of the respiratory passages were examined in progressively downward stages from the pharynx into the lungs, influenza bacilli were found with increasing predominance as the examination proceeded toward the smaller bronchi and bronchioles. In the pulmonary tissues themselves they were sometimes present in pure culture. (Compare with observations of Richard Taylor, 1918. Vide infra.) He cultivated the bacilli on haemoglobin media and described definite cultural and morphological characteristics.

The great importance of Pfeiffer's announcement naturally led to extensive work on the isolation of haemophile bacilli all over the world. The results seemed to indicate rapid and complete confirmation of his claims. Weichselbaum found the bacilli in the lungs of a considerable number of autopsies on cases that had died of bronchopneumonia secondary to typical influenza. Huber, Baümler, Kretz, Chiari found them in sputum, lungs and nasopharyngeal cavities of many typical cases. Kruse found them in 100 per cent of the early

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cases he examined. With increasing frequency the organisms were isolated not only from the respiratory passages, but from other organs in which lesions secondary to influenza had developed. Pfühl found them in the spinal fluids of soldiers that had died of meningitis, complicating influenza, and Nauwerck found them in sections of the brain in a similar cases of encephalitis. It would be possible to multiply indefinitely the accounts of similar findings. Careful investigations during these years seemed to yield positive results with such regularity that isolation of the bacillus was utilized diagnostically, and very little or no doubt concerning its etiological significance remained at the end of this epidemic. A few such accidents, moreover, as that of Kretz who infected himself from a pure culture and came down with an acute respiratory catarrh and many of the symptoms of a typical influenzal attack, appeared to remove all remaining uncertainty. Pfeiffer's original claims seemed to have been satisfactorily confirmed, and his own conclusions were accepted by most of his contemporaries.

The term "influenza" which had hitherto represented a purely clinical conception was now changed to an etiological one, and its diagnostic use was governed largely by isolation or failure to isolate influenza bacilli. This conception was further strengthened by studies such as those of Tedesco and of Scheller who found that, during the years following the epidemic period, the isolation of influenza bacilli from respiratory lesions became more and more infrequent as the epidemic receded into the past. At the same time fewer and fewer carriers of the organism were found among normal individuals. Even in patients who appeared to present the clinical picture of so-called "grippe" the bacilli became more and more rare in the course of successive years. Leichtenstern states that, in 1892, toward the end of the epidemic, a very large number of pure influenza bacillus infections of the bronchial tree occurred all over Germany, but that, in 1900, Wassermann had the greatest difficulty in finding influenza bacilli at all, even in cases clinically diagnosed as Influenza in Berlin. A similar statement in regard to work done in 1903 was made by Beck; and, indeed, most bacteriologists will probably confirm our own experience to the effect that, during the years immediately preceding the war, the discovery of influenza bacilli in the respiratory passages

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of adults, was not particularly frequent. And when it did occur the clinical condition was rarely one which could properly be spoken of as influenza.

Thus, the frequent association of the organisms with typical cases both in complicating and secondary lesions, their presence in a considerable number of normal individuals during times of epidemic prevalence and the progressively diminishing frequency of such findings in the course of the years following the epidemic, all these observations seemed to indicate clearly that the bacilli were etiologically related to the disease.

Nevertheless, during subsequent years evidence accumulated to show that even in the interepidemic period the Pfeiffer bacillus group was present in a variety of human lesions, sometimes as a harmless saprophyte, sometimes with definite pathogenic properties, and many times in conditions which had little or no resemblance to clinical epidemic influenza. It appears that after the epidemic had subsided the organism was still widely distributed among human beings, and a study of this interepidemic distribution is necessary in order that we may possess a complete picture of the pathogenic possibilities of bacteria of this group. For if we should find that these organisms can exist either as harmless saprophytes or as pathogenic agents never giving rise to typical influenza in these periods of interval, this would detract considerably from the trustworthiness of any conclusions formulated in regard to their specific pathogenic properties.

Leichtenstern has made extensive studies of the literature with the purpose of ascertaining the nature of the lesions with which influenza bacilli were most frequently associated during the years following the pandemic of 1889 to 1892. These and subsequent studies reveal an astonishingly wide distribution of the organisms, and their association with a variety of lesions second only to that of the Gram-positive cocci.

The presence of the bacilli in tuberculous processes was noted by Pfeiffer in his early studies, and since then has been observed by Ortner and many other workers. It is especially frequent when bronchiectatic cavities exist. A series of such cases was reported by Boggs, in which the influenza bacilli were apparently symbiotic with other bacteria in the cavity fluids, without being responsible for symptoms of any considerable severity.

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In the blood, at autopsy, influenza bacilli have frequently been found. Jaehle (Zeit. f. Heilkunde, 1901, XXII, 190) isolated the bacilli from the heart's blood in two of 48 scarlet fever autopsies. In 19 of these pulmonary influenza bacillus infection was present. In 23 autopsy blood-cultures of patients dead of measles, he found the influenza bacillus 15 times. In one of these he found the bacilli in the blood when the only other influenza bacillus lesion in the body was a massive infection of the tonsils. He found them 5 times in the blood of 9 cases of chickenpox, and twice in 24 cases of whooping cough. He found them also in the respiratory passages in 15 cases of diphtheria; in one of these the bacillus was present in the blood as well.

Wynekoop in 1903 studied the presence of influenza bacilli in inflammations of the larynx, pharynx and nose. In certain forms of chronic laryngitis he often obtained the organisms in pure culture. He found them in tonsillitis, and described a peculiar form of severe pharyngitis in which they were present with considerable regularity. Some of these cases simulated mild diphtheria. He often obtained the bacilli from the conjunctivae, and emphasized the fact that pure influenza bacillus infections usually tend to rapid recovery.

Madison has collected 30 cases in which influenza bacilli were grown from the blood during life. He himself reported a primary influenza bacillus bronchopneumonia in which smears from the sputum constantly showed large numbers of influenza bacilli, and in which a positive blood culture was obtained. Similar cases have been described by Meunier, Horder, Smith, Slawyk and others.

Infections of the central nervous system with influenza bacilli have been reported by Pfühl; influenza meningitis has been extensively studied by Wollstein, by Dudgeon and Adams, Saathoff and many others. A curious observation of interest in this connection has been related to us by Dr. Emmet Holt, who tells us that although influenza meningitis had not been infrequent in the Baby's Hospital in New York during the interepidemic period, he had seen practically none of these cases during the recent epidemic.

The presence of the organisms in suppurations of the nasal cavities, the orbit and frontal sinuses, has been reported in a great many cases. We have seen several examples of this, some in children, some in

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adults, in which a chronic influenza bacillus infection of the nasal cavities and antrum was apparently responsible for intermittent asthmatic attacks; and the persistence with which these organisms may remain chronically present in the deeper respiratory passages of children following bronchopneumonia, bronchitis, or whooping cough, and their apparent responsibility for prolonged cough and general malnutrition are too well known to require comment.

The bacillus has also been occasionally found in acute and chronic gallbladder infections (Heyrowsky and Kuina).

Among the most interesting studies on the association of influenza bacilli with interepidemic pulmonary disease are those made by Wollstein upon children at the Babys' Hospital in New York. In 1906 at a time about midway between the two last pandemics Wollstein published observations on children suffering from various types of respiratory infection. Briefly summarized, her results were as follows: Influenza bacilli were present in 16 of 53 cases of bronchopneumonia, and in 1 of 8 cases of lobar pneumonia, when the cultures were taken during life. Of 13 cases of bronchopneumonia studied at autopsy the organisms were found three times. They were found 6 times in connection with tuberculosis, and in isolated cases in various other conditions in which the lungs were inflamed. In agreement with other workers, she frequently found the organisms in whooping cough, and 9 times in 27 cases of measles. This last result is in keeping with many other investigations upon measles. Liebscher for instance found the organism in 11 of 57 measles cases during life, and 3 times in the lungs at autopsy; he observed a higher death rate in the influenza bacillus cases than in the others. Süsswein saw the bacilli in the nasal secretions in almost 50 per cent of such cases, and 3 times in the lungs at autopsy. Jaehle and Jochmann have made similar observations, and Albrecht and v. Preyss obtained the organisms from the lungs in post-measles pneumonia.

The great frequency of conjunctival infection with the influenza bacillus has been mentioned. It is quite probable (Williams, Wollstein, and others) that the so-called Koch-Weeks bacillus should be regarded as belonging to the group of the true influenza bacilli, and many mild and severe conjunctival inflammations have been found to be due to these organisms. Zur Nedden, Wynekoop, Williams, Woll-

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stein, and others have described a great many such cases, and Wyne koop and Wollstein particularly have reported instances in which severe hemorrhagic inflammations of the conjunctivae have shown influenza bacilli in pure culture. In some of these mild systemic symptoms were present.

It is interesting to note, that Wollstein in her extensive studies on influenza bacilli in babies has found the organisms very rarely in the throats of healthy children or in the throats of children who did not have respiratory lesions. She states that whenever the organisms were found, they seemed to exert a definite influence upon the severity of the disease. Death rates were higher, and in the bronchopneumonias with influenza bacilli there was higher temperature, greater prostration, and a longer duration of the illness. Such observations would particularly incline one to accept Ortner's opinion that true influenza may remain endemic in the intervals between epidemics as a definite clinical condition, an opinion confirmed to us on purely clinical grounds by a number of experienced physicians.

Indeed, in the intervals between large influenza epidemics there may be occasional isolated epidemics in closed institutions, such as asylums and homes for the aged. Such epidemics were reported by Sturrock in 1900, and by Nobecourt and Paisseau in 1905. Unfortunately etiological investigations of such outbreaks have yielded little additional light.

Carriers

That the carrier state may persist after infection with influenza bacilli is unquestionable. During the last epidemic Pritchett and Stillman cultivated the influenza bacillus from the mouths of 93 per cent of cases of influenza and bronchopneumonia, and at the same time they found it in 43 per cent of normal individuals. Lord, Scott and Nye during the same epidemic found influenza bacilli in 76 per cent of 34 men in the Harvard Students' Training Corps. At Camp Funston, Opie, Freeman, Blake, Small and Rivers found influenza bacilli in the mouths of 35.1 per cent of healthy soldiers. Subsequently, Winchell and Stillman found that the percentage of influenza bacilli in the throats of normal people during post-epidemic periods was as high as it was during more active epidemic stages. In 150

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individuals they found the organisms in 41 per cent. In a boys' orphan asylum in which no influenza had occurred during the epidemic, 39 per cent of the throats were positive, a percentage which was equal to that found in convalescents in an institution in which about half of the inmates had had the disease. They found carriers who had retained the organisms for four and five months after convalescence.

The experiments of Bloomfield have to a certain extent contradicated this in that Bloomfield introduced three different strains of the bacilli in large quantities into the upper air passages of normal individuals without being able to produce the carrier state. He obtained neither local nor general pathological results, and the organisms rapidly disappeared. We will recur to this work of Bloomfield below. He draws the conclusion that we can tell very little about the persistence of influenza bacilli in the throats until we know more about the subclassifications of these organisms, since he sometimes isolated, from the inoculated individuals, strains which differed in serological grouping from the strains which he had introduced. Kretz, on the other hand, found influenza bacilli in the throats of patients months after their attacks, and Rosenthal has isolated the organisms from the larynx and the trachea in about 15 per cent of the cases he examined. Davis's studies have shown the organism in 10 per cent of normal people. Klopstock found influenza bacilli in 5.1 per cent of 1000 routine sputum examinations made at a Berlin hospital, and Wohlwill has made similar observations.

We may summarize, therefore, our knowledge of the influenza bacillus up to the time of the last epidemic somewhat as follows:

During the epidemic of 1889 influenza bacilli were found in a large percentage of the cases examined, often in pure culture and in all parts of the respiratory passages. They were found in pure culture particularly in early cases, but as the epidemic trailed towards its endings and severe complications were more common, fewer and fewer pure cultivations were obtained. At this stage of the epidemic the organisms were still the predominating ones in most of the cases, but were now almost always found admixed with pneumococci, streptococci and other bacteria. They were present also in a great many of the complications which occurred in parts of the body, other than the

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respiratory tract. During the last stages of the epidemic and during the years immediately following, there seems to have been a gradual diminution of frequency of influenza bacillus findings in respiratory diseases, even in those which clinically resembled the complicated epidemic cases.

When finally it seemed that epidemic influenza had completely disappeared it was found that bacilli of the hemophile group had become established as common inhabitants of the respiratory passages of man, sometimes playing the rôle of harmless symbiants, sometimes definitely associated with pathological processes. They have been found associated with suppurations of the cavities of the head, various forms of conjunctivitis, and with a variety of other diseases. A curious development is that in pulmonary complications of conditions not primarily caused by them, they have been found with considerable regularity. Thus, they are now recognized as almost universally present in the later lesions of whooping cough and as commonly present in the pulmonary complications of measles, less commonly in scarlet fever and diphtheria. In such cases especially when they occur in children, they seem to be distinctly pathogenic, either independently causing lobular forms of pneumonia, or else as shown by Wollstein, contributing definitely to the severity of the disease.

It has also been found that the carrier state can exist at such time, and that the bacilli may be present for long periods in the nasopharyngeal mucous membranes of normal individuals or in bronchiectatic cavities without causing injury either by invasion or by toxemia.

In our final summary we will attempt to coördinate these facts with the results of more recent studies.

Recent epidemic of 1918

When we turn to the bacteriological analyses that have been made during the recent epidemic, we are overwhelmed by the wealth of reported material, but confused at the same time, by its indefiniteness in description of technique and by the frequently defective clinical characterization of the cases studied.

It will be noticed that during the early phases of this epidemic, workers all over the world failed to find influenza bacilli. Thus in

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Germany the earliest reports (Kolle of Frankfurt, Friedemann of Berlin, Mandelbaum of Munich, Citron of Berlin, and Bernhardt of Stettin) agree in failure to find influenza bacilli. Coca and Sapata made a similar negative report from Spain. Sampietro in Italy suggested the similarity of the disease to sandfly fever, owing to inconclusive bacteriological reports, and McIntosh, writing in 1918, emphasized the widespread failure to find influenza bacilli throughout the world. He himself made negative examinations on early cases in London in 1918; and similar negative results were noted in a summary in the Medical Supplement to the Daily Review of the Foreign Press brought out by the British Medical Research Committee in October, 1918. Of American workers in France the same thing was true. Indeed, the clinical picture of the cases first observed was such that there seemed to be no focus of localized inflammation from which it would have seemed profitable to take cultures. Our own experience in this respect was similar.

It must be remembered that when the epidemic first appeared, there were many who felt quite uncertain about its nature, and the systematic and purposeful search for influenza bacilli did not generally begin until an increased number of sore throats, upper respiratory catarrhs, etc., began to appear. Soon after the outbreak at Chaumont, the writer saw a similar epidemic in troops that were in the line and in reserve, and in these the presence of respiratory symptoms gave a more definite clue to the importance of cultural work on the nose and throat. In consequence, both the local laboratory officers, Lieutenants Jacobs and Avery and the writer, began to take throat cultures, and influenza bacilli were found in a considerable number of cases. Soon after this, on the writer's return to Dijon on temporary duty, a small epidemic of early uncomplicated cases was reported to Dr. MacNeal who was then the commanding officer of the Headquarters laboratory, and MacNeal and the writer obtained pharyngeal cultures from 14 of these men during the first 24 to 48 hours of their disease. None of these showed more than a mild reddening of the pharynx with very slight discomfort, and in all of them influenza bacilli were demonstrated either by smear or culture. There can be little doubt of the fact that, at least in part, the failure to find influenza bacilli in the upper respiratory secretions of the early cases must be

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attributed to two factors, first, the omission of systematic culture because of failure to recognize the disease as originating in the respiratory organs, and, second, because of inadequate technique on the parts of workers. It seems that technique was universally defective during the early phases of the epidemic, and it was not until media were improved (trypsinized blood agar was introduced in England, and modifications of what we speak of as the "chocolate" broth and agar in America and Germany) that results of reasonable accuracy were obtained. Also, a large number of workers, who had had little experience with the influenza bacillus, rapidly learned to manipulate this organism more skilfully. Following this, as the nature of the disease was recognized, a large number of analyses were made, and influenza bacilli were demonstrated in increasingly higher percentages.

It would be extremely difficult to attempt a complete review of all the bacteriological work done during this epidemic. We have selected from the literature a group of reports which are representative of the best work done in this connection during the epidemic. It has seemed useful to append to such a tabulation a statement, in each instance, of the nature of the cases and the source of the material. (See pages 236–242.)

A cursory survey of these reports shows that in the large majority of carefully investigated cases influenza bacilli were found in a high percentage of the examinations. The organisms have been present in over 70 per cent of most of the carefully studied series, and in a number of instances they have been present in over 90 per cent. Our own small group of early cases, like the series investigated by Schmidt, Deitrich and a few others, have shown the Pfeiffer bacillus in 100 per cent, and a large majority of the workers who have had occasion to study autopsies as well as sputum and nasopharyngeal material, declare that no other organism was found with comparable regularity. In many instances it was found in pure culture. Thus, Wolbach in 28 carefully studied autopsies, found it 14 times in pure culture. Dick and Murray had similar results, and Lister and Taylor in South Africa as well as Leichtentritt in Austria found it alone in no small number of their cases. Mayer, working in Vienna states that whenever he found the organisms in pure culture, the cases were mild, corresponding more nearly to the uncomplicated disease. He adds

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that he thinks that all fatal cases are due to complications, a statement which we believe to be true in general, but to which there are not a few exceptions. An interesting contribution is made by Capt. Richard Taylor, who studied the flora of the respiratory tract, from the pharynx downward toward the lungs, in cases which came to autopsy, a procedure similar to that carried out by Pfeiffer in 1891. He states that influenza bacilli were found rarely in pure culture in the trachea and secondary bronchi. Here they were usually associated with various Gram-positive and Gram-negative cocci. As he proceeded downward toward the alveoli of the lungs the bacilli were more and more free from other organisms; and in the smallest bronchi and bronchioles they were either alone or together with only one form of coccus. In the lungs themselves, however, pneumococci and streptococci predominated, though influenza bacilli were often present. We agree with the comment upon these findings made by MacNeal who takes them to indicate that the infection was primarily due to the influenza bacillus, with secondary invasion advancing along the trelisses of inflammation so produced. Similar observations have been made by Loewenthal in Vienna, and a number of other observers have laid stress upon the fact that influenza bacilli, even in complicated cases, are often found quite low down in the bronchial passages.

It is important to note that blood cultures have rarely been positive. When taken during the very early stages of the disease, or at stages in an epidemic during which the mild three day or four day fever types predominated, blood cultures have almost invariably been sterile. In severe cases occasional positive results have been obtained, but this has been rather the exception than the rule, and the great majority of blood cultures taken on severe and complicated cases of influenza have yielded either streptococci or, more often, pneumococci of one or another type.

The difficulty with most of the etiological investigations has been the inability of the investigators to select and control their material, and for this reason percentage results obtained in many cases may be misleading. The researches from which the most useful information can be obtained are those in which workers have been able to group their cases and control their material, both as to the time of the

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WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Mathews, Lancet, 1918, 2, 695	Early in epidemic broncho-pneumonia	12	Nasopharyngeal mucus	84	Concludes that influenza bacillus most frequently predominating organism. Never got positive blood cultures
Dietrich, Lancet, 1918, 2	Bronchial pneumonia	7	Autopsy material	100	None
Hicks and Gray, Lancet, 1919, 1, 419	Early epidemic cases		Nasopharyngeal swabs and sputum	70 to 80	All of the cases showed pneumococcus with influenza bacillus. Never found the organisms in pleural exudates in which pneumococci and streptococci were present. 50% of the severe cases had pneumococci in blood stream
Rose, Lancet, 1919, 1, 421	Severe cases with bronchopneumonia	24	Smears and cultures from lungs	63	These cases in British Guiana in November 1918
Lister and Taylor Pub. S. Afric. Inst. Med. Res., 1919, i, 212, April 30	Epidemic cases in Transvaal	56	Lungs and autopsy material	91	Usually associated with Gram-positive cocci, but in three cases of bronchopneumonia, Bacillus influenzae found in pure culture
Leichtentritt Deut. med. Woch., 1918, 1419	Mild and severe	Not stated	Lungs and sputum	51.6	States that he found them in the lungs in pure culture on numerous occasions, and in isolated cases in the spleen and in the brain. Rarely, but on few occasions, found them in the blood

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Neufeld and Papamarku, Berl. klin. Woch., 1919, 9. Deut. med. Woch., 1918, 1181			Smears from pharynx and tonsils	Large percentage but actual number not given	
Loewenthal, Berl. klin. Woch., 1918, 1170	Typical influenza cases (early)	85	Droplets coughed against blood plates	24	
Uhlenhuth, Med. Klinik, 1918, xiv, 777	Typical epidemic cases 2 series				At the same time took pharyngeal smears and cultures from 100 people in another region in which no epidemic has as yet occurred and found them all negative. He attributes the contrast between his favorable results and the negative ones of others to his use of Leventhal's medium, corresponding to our chocolate agar
		51	Sputum	25	
			Pharyngeal smears	25	
			First series:		
			Blood cultures, all sterile		
			Second series:		
		47	Sputum	46.8	
			5 blood cultures, all sterile		
Bergmann, Deut. med. Woch. 1918, xliv, 933	Variety of epidemic cases		Bacteriological work intensively done on 10 cases, 70 per cent positive	70	
Jordan, Jour. Inf. Dis., 1919, xxv, 28	Selected typical cases mild and severe		Material from upper respiratory tract	64	States that no single organism was constantly predominating, but that Pfeiffer bacillus is more conspicious than any other organisms and next to the diplococcus found by Mathers, at Camp Mead, pneumococcus 20 per cent of cases and Gram-negative very frequently

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WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Keegan, Jour. Amer. Med. Assoc., 1919, lxxi, 1051	Autopsy material and lung puncture	23	Smears and culture	82.6	In only 4 cases was Bacillus influenzae not found at all, and in these there was a haemolytic streptococcus. In 31.6 per cent of his cases, Bacillus influenzae was present in pure culture
MacNeal and Pease, Report to the chief surgeon, American Expeditionary Forces	Influenzae bacilli found in every case examined				
Weiss, Similar report of the 88th division, October, 1918		35	Sputum	85	
Neal, Similar report, November, 1918, Jonchery			Nasopharyngeal mucous showed influenza bacillus	90	Blood cultures of 5 cases showed pneumococcus II in two of them.
			Pneumococcus type I	2	
			Pneumococcus type II	2	
Neal and Frieberg, Similar report 26th Division, September, 1918			Nasopharyngeal smears 54 per cent positive for influenza bacilli	54	

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Holman and coworkers, Army Hospital, Pittsburg, report to the chief surgeon, American Expeditionary Forces	Of 31 cases, 24 were positive for influenza			80	These observers found influenza bacilli remaining in the nasopharynx for a long time after the disease, and consider the carrier state often established. Favorably inclined to the etiological importance of the influenza bacillus
Park, Williams and coworkers, Amer. Public Health Jour., 1919, ix, 45	1 to 200 cases examined during first to sixth day of disease				

GROUP	B. INFLUENZA			GROUP	CONTROLS			MATERIAL	AUTOPSIES		
	Present	Absent	Per cent positive		Present	Absent	Per cent		Present	Absent	Per cent positive
Hospital cases	160	40	80	Nurses, contagious	4	6	40	Lungs	24	6	80
Marines	30	0	100	Nurses, non-contagious	1	7	9	Pure culture	5	25	17
Home for children	47	1	98	Measles	4	2	67	Trachea	26	1	96
				Admission ward	4	5	41	Heart's blood	3	27	10
				Home for girls	2	32	6				
				Preventorium	14	25	33				

Okawara and Tanaka, et al., Kitasato Archives 1919, 2.	Early cases uncomplicated	Nasal secretions, sputum and autopsy material	70	

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WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Eyre and Lowe, Lancet, October 12,1918		14	Sputum	86	None
Schmidt, Munch. med. Woch., 1918, 1415	Typical complicated and uncomplicated grippe	60	Sputum and nasopharyngeal mucous	100	He states that over a year before this, that is 1917, there was an epidemic of influenza on the Eastern Austrian Front and thinks that this may be the origin of the epidemic
Mayer, Wien. klin. Woch., 1919, 82	Typical epidemic cases	210	Nasopharyngeal mucous	30.1	He states that none of the cases died in which influenza bacilli were found in pure culture. That all deaths were due to secondary pneumococcus and streptococcus infections
Gruber and Schudel, Munch. med. Woch., 1918, 905	Pneumonias, etc.	250	Autopsy material	6	These writers in the large majority of cases found Gram-positive diplococci and streptococci which they regard as secondary invaders
Loewenfeld, Wien. klin. Woch., 1918, 1274	Dead of secondary pneumonia	45	Bronchial mucous and lungs	80 in bronchial mucous. Fewer in lungs	Loewenfeld believes it extremely important to take cultures from the bronchial mucous and pus, and states that they are rarely present in the lesions in the lungs themselves
Materna and Penecke, Wien. klin. Woch., 1918, 1221	Fatal pneumonias	27	Lungs	74	Their favorable results they claim were due to great care in the bacteriological methods, to neglect of which they attribute failures of others

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Loewenthal, Berl. klin. Woch., 1918, 1170	Early cases	85	Patient's coughed upon blood plates	23	
Dick and Murray, Jour. Inf. Dis., 1918, xxv, 6	Variety of typical cases	150	Direct smears and cultures	63.2	Describes a great variation in size of the influenza bacilli in the sputum smears, and often cultivated in pure culture. Some times present in enormous numbers, and many within the leucocytes
Hamberger, Meeting Med. Inst. Chicago, Feb. 21, 1919	Cases from Camp Taylor		5 cases of pneumonia at autopsy showed pure Pfeiffer bacillus		10 cases at autopsy during 4th week of epidemic showed no influenza bacilli, but pure pneumococcus
Wolbach, Bull. Johns Hopkins Hosp., April, 1919, xxx, 104	Autopsy material at Camp Devens	28		82	Of 23 cases, he found the influenza bacillus in pure culture in 9. Of 28 cases by culture and histological methods he found B. I. in 23, and in 14 of these in pure culture. It was in pure culture in some of the later cases. In some cases in which these organisms were not in the lungs, he found them in cultures from the nasopharynx or from the middle ear. Influenza bacillus occurred with more constancy than any other organism, others being usually Gram-positive cocci
Chesney, Report to the chief surgeon, American Expeditionary Forces, 1918	Cases at Valdehan		Material from respiratory tract	Clinical cases, 46.2 positive; Contact cases, 41.6 positive; Non-contact cases, 7.1 positive	

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WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Taylor, Kenneth. Similar report to the chief surgeon	Various respiratory cases during epidemic	35	Material from respiratory tract	46	46 per cent bacillus influenzae 74 per cent pneumococcus 51 per cent streptococcus hemolyticus 87 per cent sputum bronchial pneumonia 87 per cent pneumococcus 33 per cent streptococcus

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disease at which it was obtained, and in the manner of taking. Among the most satisfactory researches in this respect are those of Park, Williams and collaborators from the New York Department of Health Laboratories. These investigators with an extensive experience of the influenza bacillus as a background, and the large material of the Department of Health available, carefully chose their cases and controls. The first group studied consisted of early cases occurring in a children's home, many in the first day of the disease. These all showed almost pure cultures of influenza bacilli. Ninety-eight per cent of the later cases in this home also showed the bacilli. The only fact which detracts from the significance of the high percentage in this series is that a number of cases of whooping cough had existed in the institution during the preceding summer. In their next group they studied 30 marines who had just come to New York in a body, and were cultured almost immediately upon the establishment of the diagnosis. In all of these influenza bacilli were found, and in these cases both whooping cough and measles, diseases with which the influenza bacillus is so often associated, could be definitely excluded. At about the same time Park and Williams obtained 34 cultures from a girls' home in which there had been no influenza, and found the organisms in two of these only. In a similar institution where there had been a number of influenza cases, 33 per cent of the inmates harbored the bacilli. Of 30 autopsy cultures, influenza bacilli were found in the lungs in 24, and in 5 of them they were in pure culture; the bacilli were also present, in considerable numbers, in 26 out of 27 tracheas examined. In 40 per cent of the cultures taken from nurses who had been in contact with cases, influenza bacilli were present, whereas, those that had not been in contact with cases showed them in 9 per cent only. Of all the studies which have resulted from this epidemic those of Park and Williams and their assistants are perhaps the most encouraging to the assumption of the etiological importance of influenza bacilli. And yet as Park himself points out, the bacilli were also found in 67 per cent of measles cases examined at about this time.

We would not be doing justice to the problem as a whole did we not include in our analysis of the bacteriological findings an account of some of the other bacteria which have been described by observers as perhaps having

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etiological relationship to the disease. In a malady in which the secondary invaders give character to a large majority of the severe cases, it is to be expected that many different organisms should be described. Mathers at Camp Mead found an unusual number of cases in which the predominating organism was a Gram-positive diplococcus probably belonging to the streptococcus group. This organism was found by Jordan in cases studied in Chicago. Orticoni isolated an aerobic non-motile bacillus from influenza cases, and from an epidemic of so-called influenza which occurred among horses in the same neighborhood. In this connection it is interesting to remember that MacNeal and Pease, in their studies of an epidemic at a Veterinary Hospital and Remount Unit at which a so-called influenza epidemic among the horses coexisted, were able to exclude any connection between the two outbreaks.

Fry in 1919 isolated oval Gram-negative yeast-like bodies from the blood of two German prisoners which upon subculture, took the form of small Gram-negative bacilli. He speaks of them as "Pfeiffer-like" organisms which, however, were not hemophylic and grew rapidly on ordinary agar. With this organism Fry and Lundie later claim to have made an antigen which gave specific complement fixation with influenza blood. Edelmann in Vienna on several occasions found paratyphoid "B" bacilli in the blood and intestines (!) of influenza cases.

The many reports in which pneumococcus and streptococcus have been found as predominating organisms we may dismiss without analysis since all investigators will now agree that no specific etiological significance can be attached to these bacteria.

Of more than passing interest, however, are the frequent reports of Gram-negative micrococci of various kinds. Most of the workers in this country have commented upon the frequency with which micrococcus catarrhalis and other Gram-negative cocci closely related to this organism have been found in influenza sputum. In our own work, especially during the Baccarat epidemic we noticed the great number of cases in which Gram-negative micrococci seemed to predominate in smears and cultures of the pharynx and throat. We were not able, however, to study these organisms in detail at the time. Kinnicutt and Binger, who worked during July and August of 1918 at an American Base Hospital in France have reported a series of cases in which the predominating organisms were true meningococci. They describe two epidemics, one which occurred at Mirmizan in the Department of Landes, in which there were 350 cases among 553 men, and 30 bronchopneumonias with 15 deaths. Another outbreak occurred at Le Courneau, Department of Gironde where there were 3915 cases with

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275 pneumonias and 65 deaths. The epidemics began as the typical mild fever, rapidly becoming complicated and ending with many severe cases. In the first epidemic they took a considerable number of blood cultures all of which were negative except one which showed meningococci of type C (Pasteur Institute serum). Four out of 10 autopsies showed meningococci in the lungs. In the Le Courneau epidemic they took 25 nasopharyngeal cultures, 22 of which showed Gram-negative diplococci. Of 14 strains so obtained, 9 were true meningococci as tested with agglutinating serum. They took 4 cultures of sputum, all of which showed Gram-negative micrococci and 2 of which agglutinated like true meningococci. Of 15 blood cultures, they obtained 4 Gram-negative diplococci, 3 of which agglutinated like true meningococci. Of 24 heart's blood cultures, 4 showed similar organisms, 3 of which were proved by serum. Of 22 cultures from the lungs, 12 showed Gram-negative diplococci, 5 times in almost pure culture; and 11 of these strains agglutinated like meningococci.

In another epidemic at St. André de Cubzac they took 29 cultures, 55 per cent of which showed Gram-negative diplococci. Only 3 of these cases showed Pfeiffer bacilli.

Fletcher in 1919 reported studies on autopsies of 36 American soldiers who died of bronchopnuemonia following influenza. In 11 of the 36 cultures taken from the lungs he found Gram-negative diplococci on blood plates, and most of these turned out to be meningococci of Gordon types I and II. Fletcher, however, also found a considerable number of cases in which influenza bacilli were present without meningococci.

Similar findings have been reported by Leitner and by Trawinski and Cori in Vienna.

It is of course difficult to make any conclusive statements about findings of this nature. There can be no question about the fact that observations so reported are accurate, and, indeed, any one who has studied the bacteriology of cases of this kind knows that the manifold nature of the flora of the respiratory passages which normally exist is tremendously enhanced in the presence of a catarrhal inflammation. It would seem to us judging from experiences such as those of Kinnicutt and Binger, from our own observations, and from reports made from various camps and base hospitals during the war that the nature of the flora of the nose and throat may take on a local character owing to infection from man to man under crowded military conditions. The predominance of streptococci in one place, pneumococci of a particular type in another, and Gram-negative micrococci at again another would necessarily influence the bacteriology of the fatal infections. During the first year of the American entrance

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into the war, this was noticed at training camps where streptococcus pneumonias or infections with pneumococci of types I or II, often predominated numerically as secondary invaders in measles, etc.

That influenza, whatever its etiology may be, increases susceptibility to invasion with all sorts of other bacteria cannot be questioned. As far as the meningococcus observations are concerned, these may well be explained by greatly increased susceptibility to this organism, induced by influenza and coincident with a high meningococcus carrier rate. Carrier rates in troops of 10 and more per cent have frequently been observed by Gordon, Glover and others, and we ourselves have seen a number of cases which began as typical influenza and ended as meningococcus sepsis or typical meningitis.

Because of the great complexity of the etiological problem we believe it wise, at the end of each block of reported data, to outline tentative summaries of the evidence so far presented. Surveying, therefore, the purely cultural work which has been done on the influenza bacillus since 1889, we may now add to the statements made in a preceding summary that the bacteriological studies made during the pandemic of 1918 and the following years have confirmed the fact that influenza bacilli may be found in a very large percentage of early and late cases of influenza; that they have been found by Park and his collaborators, by Deitrich, Schmidt and, in a similar series, MacNeal and ourselves, in 100 per cent of early cases: and that a great many of these workers have found them as the predominating organisms in cases with pulmonary complications; they have also been found by a considerable number of investigators in pure culture in autopsies of fatal cases. They have been found more frequently than any other organism in connection with the disease in all its stages.

By some investigators the organism has been found in the throats of contacts in a higher percentage than in those of non-contacts.

The failure of many investigators to find the organisms in simple cases in the early stages of the epidemic may well have depended upon the same difficulties that determined our own early failures, namely, insufficient attention to cultivation from the nasopharynx (owing to the absence of or the mild character of subjective symptoms referred to this locality) and perhaps imperfect cultural technique.

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Failure to find the organisms in blood cultures in these early cases has been practically universal, and might be considered a strong argument against the etiological significance of the influenza bacillus, because these early cases suffer from serious systemic symptoms in spite of their mild local lesions. We do not feel confident ourselves that the blood culture failures are sufficiently conclusive to warrant the assumption that the organisms are absent from the blood stream, since there have been isolated instances of positive blood culture results even in apparently uncomplicated cases. A few such have been reported by British observers during the early phase of the 1918 outbreak and there are many technical reasons why it may be very difficult to cultivate these organisms from the blood stream.

Moreover, recent observations upon the powerfully poisonous products that can be obtained in influenza cultures, made in our own laboratory by J. T. Parker and confirmed by Huntoon, Wollstein, and others indicate the possibility that a severe systemic disease may well be explained by a relatively small influenza lesion in the throat.

It is plain from cultural studies alone that the influenza bacillus is either the cause of influenza, or that it is an almost universal complicating invader, which gains a foothold in the body almost immediately upon the establishment of the original infection. The decision concerning this must eventually rest upon the same grounds that will decide for us whether the mild sore throat and bronchitis that occur in most, and perhaps in all cases, are complications or represent a part of the basic disease.

One of the great difficulties in the way of formulating final conclusions is the great frequency of influenza bacilli as harmless saprophytes and as secondary invaders in measles, whooping cough, etc., during non-epidemic periods. This, it is true, is a puzzling phase of the problem which must receive much further study. While, on the one hand it tends to weaken any positive etiological conclusions, on the other hand it might be explained by acquired immunity in the invaded subject, by fluctuation of virulence in individual strains of bacilli, or by a multiplicity of races.

The bearing of serological evidence on etiology

We might expect to obtain indirect light upon the problem of etiology from investigations of specific antibodies for the influenza

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bacillus in the blood stream of patients during and following the disease. This line of investigation has been taken up by a considerable number of workers. Thus, Loewenthal in 1918 found that his cultures were agglutinated up to 1 to 400 by the serum of his patients. He claims that the agglutination reaction may be of specific diagnostic value. Similar claims have been made by others. But there have also been a considerable number of contradictions, and during the last few months the entire question of specific agglutination in the influenza group has been in a state of great confusion. The problem is interwoven with the question of the antigenic uniformity or multiplicity of the Pfeiffer group, a problem which must be discussed briefly before we can pass judgment upon the value of the "antibody" evidence.

In 1915 Wollstein made a comparative study of different strains of the influenza bacillus isolated from various sources. She found that there was a wide difference, in pathogenic power for animals, of influenza bacilli isolated from different processes in man, Those obtained from the blood and meninges and some of those obtained from pneumonic lungs were highly pathogenic, while those from the upper respiratory passages were less so. So far as agglutination, complement fixation, and opsonin tests were concerned, there was no sharp difference between these two classes, and she concluded that in spite of differences in pathogenicity, all these organisms belonged to the same class or race, irrespective of origin. In 1919, Rappoport studied complement fixations by the serum of influenza patients with influenza bacillus antigens. He found 54.5 per cent positive fixations with sera of such cases, in contrast to a percentage of 9.67 per cent of 30 controls. Kolmer, Trist, and Yagle made similar observations on influenza cases, using a number of different antigens, one of which consisted of influenza bacilli, and found that 45 to 50 per cent of their sera reacted with the Pfeiffer bacillus, whereas 38 per cent reacted positively with streptococcus and micrococcus catarrhalis antigens. Wollstein carried out a similar series of studies, first attempting agglutination, a method which she subsequently abandoned because she found it unsatisfactory and irregular. She then did complement fixations in which she used antigens consisting both of bacilli suspended in salt solution and of heated broth cultures. By this method

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she found that normal controls did not fix complement in the presence of the antigen, but that the blood of recovered patients gave reactions in dilutions varying from 1:5 to 1:20. She found that it was necessary to use more than one strain of the organisms, in order to obtain regular results. Her reactions appeared constantly at the end of the first week, increased in intensity for two weeks, and remained demonstrable for as long as from two to four months. Of great importance is her observation that the antigens prepared with the epidemic strains were serologically similar to those produced with strains isolated from influenza cases in interepidemic years, differing from them only in quantitative relations. She draws no definite conclusions, but says: "The patient's serological reactions indicate the parasitic nature of the bacillus, but are not sufficiently stable and cleancut to signify that the Pfeiffer bacillus is the specific inciting agent." And further below: "Its presence influences the course of the pathological process."

A short time ago in our own laboratory similar complement fixation tests were carried out with convalescent influenza sera by Mrs. Parker, experiments in which as many as six different antigens were used on every serum. It was found that a large number of supposedly normal sera gave fixations as powerful as those obtained from convalescent cases. Although the cessation of the epidemic prevented the completion of this work, it was so carefully done and controlled that it has persuaded us that complement fixation is at any rate not sufficiently sharp to throw conclusive light upon the problem.

An astonishing and confusing turn has been given investigations of this nature by the agglutination experiments carried out by Valentine and Cooper in the New York Department of Health Laboratories. These workers isolated organisms from autopsies and active influenza cases and then attempted to classify them by agglutination reactions. Their primary purpose was to find out whether there was any single epidemic strain, and they paid particular attention to those strains which were obtained from lungs at autopsy and other lesions in which it seemed fairly definite that they were not dealing with saprophytic habitual symbiants. It is impossible to detail all their results, but it is sufficient to say that they found a surprising multiplicity of races. The following examples may suffice to indicate the degree to which

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this was true. Of 10 autopsy strains no two were found alike by agglutination. One autopsy strain was identical with one of the miscellaneous strains, and another autopsy strain was identical with another of the micellaneous ones. Of 73 miscellaneous strains, no two were found to be identical. Of 54 strains obtained from military patients, only 2 strains from different individuals were found identical. But in one case the third day isolation was identical with the seventh day, but the one on the fourteenth day was different. Of 28 strains obtained from a Hebrew orphan asylum only 2 were found to be identical. And of a family of 6, from each member of which an organism was obtained, all the strains were found to be distinct. Park states that in 9 of the autopsy strains the "unlikeness" of the strains was so sharp that absolutely no cross-agglutination took place.

Bloomfield who introduced influenza bacilli into the nasopharynges of normal people, states that in 5 instances which he isolated influenza bacilli more than twenty-four hours after he had introduced them, the organisms recovered differed from those introduced, the tests applied being the biological differential methods suggested by Rivers. The strain introduced was in some cases an indol former and agglutinated with stock sera, whereas the recovered strain formed no indol, and did not agglutinate with the serum. In another case the strain introduced was non-hemolytic and formed no indol, whereas, the one recovered from a tonsillar crypt after four days was hemolytic and formed indol.

It is plain even from the few investigations that we have mentioned that no help can be expected at this time from serological investigations. The agglutination reaction is obviously useless for this purpose at the present time. When investigators as careful and experienced as Park and Williams and their assistants report six different agglutination types from six members of the same family, the first thought that comes to us is not that these strains are all different, but rather that agglutination in this group, for some reason or other (perhaps because of the minuteness of the organisms, and peculiar surface tension relations), is not specific; and the frequency with which normal sera have fixed with influenza bacillus antigens of six different races in our own laboratory, leads us to believe that complement fixation too is a method of small promise in this problem. And even

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though specific antibody reactions could be regularly observed in active and convalescent cases, it is doubtful whether this would show much more than the organism is pathogenically significant; whether as the original etiological factor, or as a secondary invader, however, would still be in doubt.

Evidence derived from vaccination

Another set of observations which must be included in our consideration of the etiological importance of influenza bacilli, are those which deal with artificial immunization or vaccination, prophylactically employed during influenza epidemics. Such evidence would possess the same indirect value as antibody investigations, in that protection with influenza vaccines would indicate specific relationship. Such investigations are fraught with many possibilities of error, since during an epidemic it is difficult to safeguard the vaccinated and the controls from accidental infection, and to impose upon them conditions which would approach experimental accuracy.

The general impressions of Park who thoroughly realizes the difficulties attending accuracy in such work, are unfavorable to the assumption of any protective effect.

Eyre and Lowe inoculated 16,000 men, leaving 5700 controls which were either uninoculated or had received only one dose. The vaccines contained pneumococcus, streptococcus, influenza bacilli, staphylococcus aureus, micrococcus catarrhalis, Friedlander bacilli and a bacillus which they call bacillus septus. They tabulate their results as follows:

	per cent
Incidence among inoculated	1.3
Incidence among uninoculated	4.1
Mortality among inoculated	0.26
Mortality among uninoculated	2.2

Cadham in 1919 reported studies in which he used mixed vaccines of streptococcus, pneumococcus and influenza bacilli upon soldiers. He claims that the incidence of pneumonia was one-half and the mortality less than one-third among the inoculated as compared with the uninoculated. The mortality of inoculated soldiers was 2.5 per 1000, whereas, in the town nearby among the general population it

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was 6.28 per 1000. This particular experiment proves nothing in our opinion, since the mortality in influenza is generally due to secondary infections, and since the soldiers were all vigorous young people, while the inhabitants of the town included the aged, tuberculous and very young.

Wirgman in the same year reported observations upon 11,000 people of whom 800 were inoculated in November and December, 1918, and January, 1919. His figures are as follows:

	per cent
Incidence among inoculated	5
Incidence among non-inoculated	10
Death rate among inoculated	0
Death rate among non-inoculated	19

Friend reports observations at a public school in West Horsham made during this epidemic. Of the boys 633 were inoculated and 186 uninoculated. The school remained free of influenza, although the disease was prevalent in West Horsham itself. But it is recognized by Friend that physical training, careful supervision, hygiene, and good nutrition played important rôles in holding down the sick rate.

McCoy in a criticism of vaccination in influenza has pointed out a number of significant sources of error in such investigations. The chief one of these lies in the fact that the inoculations have usually been done during the progress of an epidemic and that the case-incidence among the inoculated has been compared with the case-incidence among the general population or controlled groups calculated from the beginnings of the epidemic. It is obvious that a number of the cases in the general population may have occurred before the vaccine was given, and among the vaccinated are included a number of people who are probably insusceptible. Also he points out that a vaccine cannot ordinarily be expected to have any appreciable prophylactic effects in less than seven or ten days after it is given, and considers that the only fair comparison is one which takes into account calculations on vaccinated and unvaccinated beginning ten days after the vaccinations have been made. In summarizing the evidence he selects a number of instances in which these criteria have been observed. Thus Hinton and Kane vaccinated about one-half the patients is an epileptic colony, the vaccinations being completed

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some ten days before the disease became prevalent in the institution. The vaccine contained 8,000,000 bacilli per centimeter, and a total of 2,000,000,000, was given to each person. There were 461 people vaccinated, and 538 not vaccinated. Among the vaccinated, there was a morbidity of 35.4 per cent, with 17 per cent deaths, while among the unvaccinated there were 34.3 per cent cases with 13.5 per cent deaths. A similar experiment was done on naval personnel at the Pelham Bay Training Station (Notes on preventive medicine for medical officers, United States Naval Bulletin, nos. 50 and 51). Nine per cent of the 154 inoculated, and 5 per cent of the 800 uninoculated developed the disease. Similar results were obtained at a naval base in South Carolina. McCoy reports a few experiments carried out in various institutions by members of the United States Public Health Service in which a comparison between 484 vaccinated and 842 unvaccinated controls were made. Among the vaccinated there were 31.6 per cent cases, with no deaths, and among the unvaccinated there were 26.3 per cent cases with 1.8 per cent deaths. In this case the vaccine was a pure influenza bacillus suspension.

We may summarize this phase of the work, in complete agreement with McCoy, to the effect, that, in spite of the general impression favoring the value of vaccination in the prevention of influenza, gained from the study of poorly controlled experiments, the evidence furnished by experiments that have been controlled in every particular has so far failed to demonstrate any effects whatever upon either incidence or mortality.

Inoculation experiments

The most perfect proof of the etiological relationship of influenza bacilli with the disease could of course be obtained by the production of the typical disease in normal human beings by inoculation with pure cultures of influenza bacilli. During the earlier pandemic it seemed that certain laboratory accidents had definitely indicated that such transmission was possible, the one most frequently cited being the laboratory infection of Kretz whose nose touched a plate he was fishing, and who in consequence developed an acute inflammation of the respiratory passages with influenza bacilli persisting in his sputum for several months. In such cases, however, just appraisal of the

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evidence is difficult because these accidents occurred during an epidemic or its early post-epidemic periods and happened to individuals the nature of whose work brought them into contact with infectious material. Also the symptoms described were usually those of localized catarrhal inflammations rather than of true influenza. Purposeful and well controlled experiments upon man would be more conclusive and extensive attempts in this direction have accordingly been made by a number of investigators during the last pandemic.

Since typical influenza cannot be produced in any of the lower animals, the only species which besides man are worth considering for such work are the monkeys and the higher apes. Within recent months Cecil and Blake working at the United States Army Medical School in Washington, have succeeded in producing typical lobar pneumonias by intratracheal inoculation of pneumococci in various species of monkeys. This encouraged them to experiment upon these animals with pure cultures of influenza bacilli. They used a Philippine monkey, Macacus Syrichtus, and a Central American species, Cebus Capucinus. The strains of Pfeiffer bacilli employed were isolated from an influenzal pneumonia in a child. The virulence of the strains, which has been on artificial media for six weeks, was raised by successive mouse passages and subsequent intraperitoneal passage through a series of 13 monkeys. They then inoculated a group of 22 monkeys. The material used for inoculation consisted of first or second subcultures of organisms isolated from animals dead of pneumonia or peritonitis, and of peritoneal exudates from such animals, used directly from the body.

In some monkeys the material was introduced into the nose by application with a sterile cotton swab or with a pipette. In another group the material was introduced low down into the trachea by injection with a syringe.

Twelve monkeys were inoculated by the nasal method and in every instance acute respiratory disease developed; three to five hours after inoculation there was prostration, in some cases with a temperature of from 103° to 106°F. in others there was very little or no fever. Sneezing, rubbing of the nose and other signs of catarrh became manifest. In most cases at the end of twenty-four to forty-eight hours the infection spread to the lower passages and a cough developed.

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Five of the monkeys developed acute sinusitis from which the influenza bacillus could be obtained. Two animals developed pneumonia on the third and fourth days, and the influenza bacillus was obtained in pure culture from the lungs. Ten monkeys received intratracheal injections of 1 to 5 cc. Again prostration and temperature developed in most of them with respiratory symptoms. In one case general infection with speticemia and pericarditis ensued. None of these died. Seven developed pneumonia and were killed during the active stage, and from the lungs influenza bacilli in pure culture were recovered. The pneumonia which developed was widespread, and lobular in type, with extensive hemorrhage and edema appearing to Blake and Cecil similar to that occurring in man.

The experiments of these investigators show that the bacillus of influenza can produce a violent infection of the upper respiratory tract with catarrhal symptoms and other manifestations, common in man at the time of prevalence of influenza epidemics. There can be no doubt about the fact that these experiments add considerable weight to the assumption that the bacillus of influenza causes the disease in man. We will recur to this in our final discussion of this phase of the general evidence.

More directly pertinent are inoculation experiments on man. David J. Davis in a letter written to the Journal of the American Medical Association of May 3, 1919, writes that in 1906, having isolated influenza bacilli from a considerable number of cases of whooping cough, measles and varicella, he inoculated a young healthy man with pure cultures of the bacilli. Preliminary cultures showed no similar organisms in the subject's throat; he had had no serious illness of any kind within the immediately preceding period. The washings of 6 blood agar tubes were taken up in salt solution and the throat, tonsils, and nasal mucosa were smeared with the suspension. Forty-eight hours after the inoculation he complained of chilliness and great weakness. A temperature of 100.2° developed, but rapidly subsided, returning to normal on the third day. He complained of headache, general malaise, and coughed slightly. The throat was slightly congested, and the pharynx coated with thick, stringy mucus. The local condition persisted for about four weeks during which there was a very slight cough which did not in any sense resemble that of

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whooping cough. During the first few days an almost pure culture of influenza-like bacilli was recovered. In the course of the next three weeks the influenza bacilli gradually disappeared from the throat. There were no complications. The description of this case, as given in Dr. Davis's letter has certain important points of similarity with early cases of epidemic influenza, especially as regards the mildness of the local symptoms with the sudden development of temperature, severity of the systemic symptoms and short duration of the fever.

In 1919, Rosenau, McCoy and collaborators, working under Government auspices, carried out a series of important experiments on man carefully controlled and elaborately planned. The group conducting the investigation were officers of the United States navy and of the Public Health Service; McCoy, Goldberger, Leake and Lake on the part of the Public Health Service, coöperating with Rosenau, Keegan and Richey, on the part of the United States navy. The experiments were carried out at Gallops Island, the quarantine station near Boston. The volunteers were all between eighteen and twenty-five years of age and in good physical condition. Of the 100 men used, none of them had had influenza or any febrile attack during the preceding winter. Preliminary experiments in which pure cultures of the influenza bacillus in moderate amounts were instilled into the nostrils of a few of the volunteers were entirely negative. In consequence, a more drastic experiment was decided upon. Nineteen volunteers were given a considerable quantity of a mixture of 13 different strains of Pfeiffer bacillis, some of them recently obtained from the lungs at autopsy, others representing subcultures of different culture-generations obtained from recent cases. Suspensions of the bacteria were sprayed into the nostrils, eyes, and throats with atomizers while the volunteers were inspiring. Several billions of the organisms were used on each one, but not a single one of them developed any kind of illness.

Following these negative experiments an attempt was made to infect directly with mucous secretions obtained from the mouths, noses, throats, and bronchi of active cases of influenza. The material was obtained from febrile cases by washing out nostrils and throats with 5 cc. of salt solution and allowing the patient to blow his nose

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vigorously into a sputum dish. They were then made to gargle with some of the solution and this was added to the rest. Bronchial mucus was obtained after coughing, and the nares and throats were swabbed. The swabs with all the materials were then put into bottles with glass beads, and this (properly called "stuff" by Rosenau) was administered to the volunteers. Ten men were used and each of them received about 1 cc. sprayed into nose and throat while inspiring, and into the eyes. None of them became sick. Other experiments done at this time by the same Board will be recorded when we come to speak of filtrable virus. Most astonishing of all of the work done by this Board are the entirely negative attempts to infect such volunteers by bringing them into the closest possible direct respiratory contact with cases in the active stages of the disease.

McCoy and Richey carried out similar experiments at Goat Island in San Francisco Harbor, also with entirely negative results.

It is very difficult to comment upon these experiments. Their completely negative character would lead one to assume not only that influenza bacilli did not convey the disease, but the upper respiratory secretions of influenza patients were not the vehicle of infection. The latter conclusion can hardly be credited in view of the large volume of epidemiological evidence in favor of such transmission; and when we consider the experience and reliability of the investigators who carried out these experiments we must assume that some third factor, the most likely one being insusceptibility on the part of the volunteers must have played a part. Even this, however, would seem unlikely in view of the large number of men used and the careful scrutiny made before the experiment. As a matter of fact there is no satisfactory explanation for these failures at the present time.

Wahl, White and Lyall in 1919 also applied saline emulsions of fresh Pfeiffer strains from epidemic influenza cases to the nares and nasopharynges of 5 healthy men, absolutely without success; and these investigators did not succeed, except in a single case, in recovering the influenza bacilli from the nares forty-eight hours later. To this point we will refer in our summary since we consider it of considerable importance.

Bloomfield, investigating more particularly the length of time during which influenza bacilli would persist in the upper respiratory pas-

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sages of healthy individuals, introduced 3 different strains of influenza bacilli in large amounts into the upper air passages, and in none of his 5 cases observed any local or general pathological effects. Moreover Bloomfield found that the organisms disappeared within from one to two days, and that a carrier state was produced in none of them.

Yamanouchi, in connection with his experiments on filtrable virus, has reported completely negative experiments with the Pfeiffer bacillus in man.

Lister and Taylor though unsuccessful with filtered material, inoculated 5 controls with unfiltered material from influenza lungs. Two of these had typical attacks of influenza, coming down with the disease thirty-six hours after the material had been instilled into the nasopharynx. One volunteer was sprayed with a pure culture of influenza bacilli and came down with a "mild attack."

More recently, Cecil reported to the Medical Section of the New York Academy of Medicine (May 19, 1920) a few experiments in which he introduced Pfeiffer bacilli (the virulence of which had been raised by methods analogous to those used in his previous monkey experiments) into 6 persons. He obtained moderate local and systemic symptoms which suggested very mild influenzal attacks, curiously enough there was absolutely no temperature in any of them.

Attempts to produce typical influenza with cultures of influenza bacilli have, therefore, been negative in most cases. With the exception of the few instances of apparent success by Lister and Taylor and the last suggestive experiments of Cecil no encouragement has been obtained along these lines. But it should be remembered that it has been shown that it is extremely difficult (as in Bloomfield's work) to induce the influenza bacillus to gain a foothold on the normal mucosa, and negative experiments cannot be taken as conclusive until a failure to obtain symptoms persists in spite of the establishment of the organisms in the inoculated throats for at least forty-eight to seventy-two hours.

Filtrable virus

Before we can attempt to summarize views on the etiological importance of the influenza bacillus, it becomes necessary to consider in some detail a series of investigations inspired by the suggestion that influenza may be due to a filter-passing virus.

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The thought that such a virus might be responsible for influenza is suggested by the nature of the mild cases which appear early in epidemics, the extreme infectiousness of the disease, and the lack of uniform bacteriological findings in such early cases. Moreover, the clinical similarity of the catarrhal features of mild grippe with the ordinary common cold, in which the work of Kruse, Foster and others has indicated a possible "filtrable virus" etiology aroused hopes of similar "leads" in the influenza problem.

In October, 1918, at the Academy of Sciences in Paris, Nicolle and Lebailly made a preliminary report on studies which later they described in detail in the Annales of the Pasteur Institute. These workers first inoculated mice and guinea pigs, intraperitoneally and intracerebrally, with blood and secretions from a typical case of uncomplicated grippe. These attempts were unsuccessful. They then inoculated nasal and buccal secretions of a typical case into the conjunctiva and the nasal cavities of several monkeys (Macacus Sinicus) using the secretions both filtered and unfiltered. At the same time they inoculated two healthy human beings. The monkeys became sick in six days with a temperature of 40°C. and with diarrhea and great depression. Both of the human beings who had been subcutaneously inoculated with the filtrate became ill at about the same time, and in the same way as the monkeys. Blood from the first monkey was injected into a man twenty-two years old without result.

Subsequently, they injected blood of a typical case into a man intravenously. The result was doubtful, but this subject was older than the others, a fact to which they attribute their partial failure. They concluded that: (1) Influenza secretions are virulent. (2) Macacus sinicus and Cynomologus are susceptible by conjunctival and nasal inoculation; (3) the agent is filtrable since the filtered secretions produced disease in 2 human beings after subcutaneous inoculation. (4) intravenous inoculations and blood inoculations are unsuccessful; (5) virus is easily destroyed by drying or by prolonged exposure to conditions outside the body.

At about the same time Dujarric de la Riviere took blood from 4 severe influenza cases and after dilution filtered it through Chamberland filters. He injected himself subcutaneously with 4 cc. of this

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filtrate. On the third day after the inoculation he developed intense headache, pains in the limbs, chilliness and weakness. His temperature went to 38°C. and fluctuated from then until the fifth day, after which he rapidly improved; great weakness and cardiac disturbances remained. He seemed to be immune to subsequent inoculations of the sputum filtrate sprayed into his nose and throat.

Selter in 1918, failing to find influenza bacilli with any regularity, tried the same thing. He filtered nasopharyngeal mucus and gargle water of patients early in the disease, through Berkfeld filters, and sprayed his own throat and that of a woman assistant with this material, both of them inhaling the spray. In both cases a "mild influenza" resulted within seventeen to twenty hours.

Binder and Prell in the same year described minute bodies smaller than cocci in the tissue spaces around the vessels of the lungs in all cases of influenza and failed to find similar bodies in other pulmonary infections. These coccoid bodies were as small as those described by Noguchi in poliomyelitis, and could be stained by iron hematoxylin and Giemsa, but not by Gram. They believed that they could cultivate these bodies in serum-sugar-broth, but were extremely cautious in drawing etiological conclusions.

V. Angerer, soon after this, inoculated rats with the serum of influenza cases. When the animals became sick he filtered their blood, and cultured the filtrates in glucose bouillon. In these cultures he found minute granules similar to those described by Binder and Prell. Similar bodies he claims to have cultivated directly from the serum of human influenza cases. He, too, was extremely cautious in drawing conclusions from these findings.

In October, 1918, Bradford, Bashford, and Wilson published results of studies upon six diseases including trench fever and influenza in which they claimed to have shown that filter-passing organisms were involved in all of them. With their filtrates they produced illness in guinea pigs and monkeys; and in anaerobic cultures prepared by a modification of the ordinary technique employed for Treponema pallid they observed certain small Gram-positive bodies which they regarded as the causative agents.

Similar, though less extensive experiments were reported by Gibson, Bowman and Conner.

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Later, Arkwright who had been working along the same lines criticized the results of Bradford, Bashford and Wilson, reporting negative experiments carried out by the war office upon three volunteers inoculated with the supposed cultures of Captain Wilson. He also pointed out the frequency of the appearance of small coccoid bodies in control tubes of media prepared by the method used by the other investigators. Indeed, the almost regular observation of cloudiness and of minute coccus-like bodies in tubes prepared by the anaerobic method mentioned above has puzzled many workers in the past. We have noticed it again and again in work with syphilis and poliomyelitis and are quite sure that it is dependent upon the action of the tissue enzymes upon the protein of the medium. Bradford and Wilson admit the inconclusiveness of their results, at least as far as the minute bodies are concerned, in statements appended to Arkwright's article.

In 1919, Yamanouchi, Sakakami and Iwashima reported experiments on the filtration of influenza virus which, if they could be completely accepted, would settle the entire matter, conclusively. These results were as follows:

1. An emulsion made of the sputa of 43 influenza patients in Ringer's solution was injected into nose and throat of 12 healthy people.

2. Filtrates of the same emulsion was injected into noses and throats of 12 other healthy people. Six who had already had influenza showed no symptoms, but all of the other 18, those who had had the emulsion and those who had had the filtrate, came down with the disease after an incubation of two to three days.

3. Filtrates of blood of influenza patients were injected into noses and throats of 6 other healthy people with similar positive results.

4. Filtrates of sputa were inoculated into 4 healthy people; and 4 others received filtrates of the blood of influenza patients subcutaneously. All of them developed the disease after two or three days with the exception of the one who had had influenza.

5. A pure culture of Pfeiffer bacilli and a Pfeiffer bacillus culture mixed with pneumococci, staphylococci and streptococci was injected into nose and throat of 14 healthy people who had not had influenza. No symptoms followed these injections.

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Lister and Taylor working in South Africa filtered material from the lungs and throats of typical influenza cases and instilled the filtrates into the nostrils and throats of human volunteers and monkeys. *All were negative.* Of 5 controls receiving unfiltered material, 2 had typical attacks of influenza 36 hours after inoculation. All the monkeys, even those that received unfiltered material, remained well. They sprayed the nasal passages of one volunteer with a pure culture of influenza bacilli, and in this case a "mild attack" resulted.

Wahl, White, and Lyall in 1919 sprayed the nasopharyngeal cavities of several men with Berkfeld filtrates of material from pneumonic lungs of typical influenza cases, with entirely negative results.

Leschke, in the same year, used bronchial secretions and juices expressed from the lungs of influenza cases and filtered them through Berkfeld filters. He inoculated these into ascites broth. After forty-eight hours, minute round bodies were noticed which could be stained with heated concentrated carbol fuchsin and were Gram-negative. They could not be transferred successfully to new cultures, but these minute bodies were also visible in bronchial sercretions of dead influenza cases as well as in lung sections. Lung filtrates, incubated for several days and vaporized, were inhaled by a number of people for several minutes. These individuals came down with "typical influenza!"

Fejes (in 1919) filtered the sputum of influenza pneumonia cases and injected it subcutaneously into rabbits and guinea pigs without result. The same material was injected on four separate occasions into monkeys, two monkeys being used in each experiment. In these cases one monkey was injected with the material immediately after filtration, and the other after heating for one hour at 65°. The animals that received the heated filtrate remained well. All the monkeys treated with the unheated filtrate died several days after the inoculation, with clinical and pathological appearances of general hemorrhagic sepsis. The material from which the filtrates were made showed in one case a pure pneumococcus, in the second a streptococcus hemolyticus, and in the other two mixed cultures with Pfeiffer bacilli. The bacteriological analysis of the animals that died is unsatisfactory as described.

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Minute bodies in smears of throats, noses and exudates of influenza cases also have been described by Kronberger and Poppelmann.

Experiments made by the United States Public Health Service and the United States navy under the direction of Rosenau and McCoy are among the most extensive that have been carried out upon human beings. They have been referred to, in part, in a preceding section. After unsuccessful attempts to produce the disease with pure influenza bacilli, they instilled filtered nasopharyngeal mucus from fresh cases into the tonsils, throats and eyes. The results were entirely negative. Subcutaneous inoculation of similar filtrates into 10 volunteers, each one receiving 3 cc., were entirely unsuccessful. Negative results were also obtained when blood was injected and when the volunteers were brought into close respiratory contact with active cases.

In the May 29 issue (1920) of the Journal of the American Medical Association, Olitsky and Gates published a series of experiments also dealing with a filtrable infectious agent in influenza. They used filtered and unfiltered influenza secretions, and filtered and unfiltered lung tissue suspensions prepared from previously inoculated rabbits. The inoculations were carried out directly into the lungs by means of the intratracheal catheter, 3 cc. of the material being used for rabbits weighing from 2½ to 3 kgms. From 7 to 8 fresh cases, that is cases less than thirty-six hours old, they obtained definite effects in rabbits which they describe as follows: Within twenty-four to forty-eight hours after inoculation, fever developed, with listlessness and general illness of the animal. With this there was conjunctivitis and a marked leukopenia. These symptoms lasted for about three days, after which the animal returned to normal. They never died except in cases where obvious secondary infection had taken place. When killed during the period of illness, the respiratory organs alone showed pathological changes. The lungs were enlarged and edematous, and often hemorrhagic. There were hemorrhagic foci on microscopic sections, and there was a cellular exudate in the alveoli. Controls made by many different methods failed to show similar effects. After this, repeated filtration did not interfere with the effects described above. The agent, whatever it was, seemed to resist 50 per cent glycerine for nine months. They draw very conservative conclusions.

Since the first writing of this paper, Olitsky and Gates have con-

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siderably extended their researches by further animal inoculations and cultivation experiments by anaerobic methods corresponding to those used in treponema cultivation, namely, anaerobiosis with tissue and ascitic fluid. They have cultivated from filtered nasopharyngeal washings of influenza patients in the first thirty-six hours, a minute bacilloid body capable of indefinite propagation on artificial media, which they have named the bacteria pneumosintes because of its peculiar pathological reactions in lung tissue. They have also recovered this organism from the lungs of infected rabbits. This minute Gram-negative bacillus-like organism is apparently strictly anaerobic and retains its virulence for rabbits for only a limited num ber of generations after cultivation from the human body. They obtained it again during the short influenzal wave of the past winter, 1921–1922, and the characteristics of this organism are similar to the original one. After prolonged cultivation, the organism appears considerably larger than one would expect from a filtrable virus, but still they continue to obtain growth from filtrates through N and W filters. Similar but distinctly different organisms of a somewhat larger size and slightly fusiform appearance were obtained from common colds and normal throats. There seems to be no doubt in the writer's mind, after seeing their cultures, that Olitsky and Gates have observed a group of organisms hitherto undescribed, and the relationship of the true pneumosintes to early influenza, its apparent preparatory influence for secondary infection must lead one to take it seriously as one of the possible etiological suggestions. The difficult nature of the entire problem, however, does not permit acceptance of this, though strict attention to their methods and results will be necessary for all investigators who approach the influenza problem when another wave becomes eminent.

Summary of evidence bearing upon etiology

In the course of every scientific investigation, it becomes necessary, from time to time, to classify and analyze the available data in order that there may be a clear differentiation between experimentally determined facts, probabilities amenable to further experimentation and pure surmise. It is a systematization not only of our knowledge but of our ignorance as well. For in subjects as involved as are the

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problems of influenza, on which so many different people have written from so many different points of view, the few available facts may easily be lost in an accumulation of clinical and experimental slag.

Conclusions cannot be drawn. But we can segregate the obviously misleading from the proven facts and can perhaps formulate more clearly the directions of study which appear most promising of eventual light.

It is entirely in this sense that we submit the following summary:

Influenza in its simplest clinical form is a mild fever, with sudden onset, characteristic pains in head, back, and limbs, great prostration and a fever curve which rarely lasts longer than three or four days. It is in this form that it usually makes its first epidemic appearance, and, at this stage, causes almost no mortality. The slight sore throat, mild bronchitis and injection of the conjunctivae which are present in a large number of the cases may represent secondary infections or complications, but are more probably characteristic features of the basic disease.

It is the causation of this basic condition which constitutes the true etiological problem of influenza. While it is generally acknowledged that the influenza bacillus appears early in the disease and is present with considerable regularity, it has been suggested that, preliminary to this, there may be infection by some other agent, perhaps a filtrable virus which paves the way for secondary invasion, first by the influenza bacillus, followed by other bacteria habitually present in the upper air passages.

In favor of attributing the entire process to influenza bacilli are: The frequent isolation of the bacilli even from the earliest and simplest cases; the high percentage of influenza bacillus isolations from all varieties of early and late complications; the peculiar distribution of these bacilli in the large and small bronchi in fatal cases; their frequent presence in pure culture at autopsy; the wide distribution of the organisms throughout populations at times of epidemic, and their gradually diminishing frequency in normal and diseased respiratory passages as epidemics fade into the past. Recently acquired knowledge, furthermore, regarding the potent poisons formed by influenza bacilli in culture, permits us to account for the entire clinical complex of the simplest variety of case by the establishment of a relatively

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small influenza bacillus focus in the throat or nasopharynx of a susceptible individual.

Against the assumption of the etiological importance of the influenza bacillus are the frequent failures of competent bacteriologists to find the organisms in the early cases, the presence of the bacilli in the throats of normal individuals; their presence in pathological conditions obviously not clinical influenza; their frequent presence as complicating invaders in whooping cough, measles, etc., the antigenic multiplicity of strains isolated at times of epidemic; and the infrequency of positive blood culture findings in early cases. None of this negative evidence is conclusive for reasons that have been indicated in the text.

Investigations on the appearance of antibodies in the serum of cases that are sick with or convalescent from influenza permit of absolutely no conclusions at the present time, owing to the irregularity in antibody reactions done with influenza bacillus antigens, whether the method used be that of agglutination or that of complement fixation. The curious results obtained by Cooper and Valentine show either an enormous multiplicity of influenza bacilli or non-specificity of the agglutination reaction with this group. Experiences with complement fixation have not given uniformly reliable results when human sera were used. Moreover, were we to find an increased concentration of antibodies against influenza bacillus antigens, it would serve to prove nothing more than the pathogenic significance of the influenza bacilli which we know from cultural studies to be present in most cases, and would not help us to decide whether the organism were the primary cause of the disease or merely secondary invader. It would show nothing more than do the frequent positive serum reactions which have been obtained in influenza and in some other diseases with streptococcus antigens.

Protection experiments with vaccines have been absolutely inconclusive; indeed, they seem to indicate that influenza vaccines do not protect to any considerable degree. This, however, throws little light upon the etiological problem since successful vaccination is delicately dependent upon manner of vaccine production, dosage, mode and frequency of administration, and has yielded negative or doubtful results even in diseases in which the etiological problems are settled.

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Attempts to produce the disease in human beings with pure cultures of influenza bacilli have been in general unsuccessful. There are, however, a few very suggestive experiments in the literature particularly the isolated cases of Lister and Taylor, of Wahl, White and Lyall, that of Dick and the more recent ones of Cecil, which at least show that occasionally mild systemic illness may follow the introduction of the bacilli. The completely negative results of Rosenau and McCoy and their collaborators, of Yamanouchi and others are discouraging, but if we consider that in such experiments two factors must be simultaneously adjusted to each other in a perfect way, namely, the virulence of the strain and the susceptibility of the individual, it may well be that failure of one or the other of these prerequisites may account for many negative attempts. It is worth noting in this connection, too, that in many cases where negative results were obtained the organisms rapidly disappeared from the nasopharyngeal mucosae of the inoculated individuals; whereas, in those that partially succeeded, as well as in some accidental infections with cultures the organisms remained present for some time, showing that in the former they were quickly removed by the protective mechanism, whereas, in the latter, they were able to establish a foothold.

Although the burden of the evidence so far cited seems to point in the direction of probable causation by the influenza bacillus, it is obvious that there are a number of elements of uncertainty. To these there is added, as a very serious objection, the report from several sources which cannot be ignored, of successful production of an influenza-like disease in human beings with filtrates of influenzal material—the conditions so produced cannot be positively identified as true influenza. Nevertheless, they are sufficiently suggestive to necessitate further experimental study.

This leaves the entire subject in a very unsatisfactory condition. The temptation to draw definite conclusions from material of this kind is always a strong one. But to profess certainty when available evidence does not justify definite conclusions is as serious an error as to put forth inconclusive experimental work, and would serve merely to mask the truth.

One thing seems distinctly worth emphasizing in closing a discussion of influenzal etiology at the present time, and that is the advisa-

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bility of constant attention to the entire influenza literature on the part of bacteriologists working in well equipped laboratories with assistants and equipment sufficient to attack large problems of this kind when occasion arises. The problem of influenza etiology will not, in our opinion, be solved at times when influenza epidemics are in full swing or in their secondary or tertiary waves. Solution will come from laboratories that are prepared to pounce upon the opportunity when epidemics are in their adolescence, and bacteriologists will miss this opportunity of swinging their equipments and energies for a few intensive months into this extremely important problem unless they are familiar with the clinical aspects of early influenza, such as we have outlined it in a previous paragraph, and unless they are thoroughly and critically familiar with the important etiological work that has been done. This alone we would regard as sufficient excuse for an inconclusive summary of etiological studies such as that in the preceding section.

THE EPIDEMIOLOGY OF INFLUENZA

Former epidemics

In diseases like smallpox, diphtheria, scarlet fever, etc., in which sharp clinical and etiological definition is possible, epidemiological data can be obtained with considerable accuracy. In influenza such studies are rendered incomparably more difficult because of the diagnostic difficulties emphasized in preceding sections, and because of the complete lack of any etiological criterion of recognition. During periods of epidemic and especially during the initial stages of outbreaks, the diagnosis of the disease can be established with a considerable degree of certainty. But the widespread catarrhal infections of many different causations, which accompany such epidemics and bring about generalized opportunities for interchange of respiratory organisms, lead to an increased morbidity in which many factors besides the influenzal ones are involved.

Particularly confusing are the problems of recognition in the interepidemic periods during which physicians are forced to use the terms "influenza" and "grippe" upon vague clinical grounds, fully conscious of the diagnostic uncertainty which such a terminology

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entails. As we shall see, epidemiologists have been forced for these reasons to base many of their calculations upon atypical fluctuations in seasonal curves of the morbidity and the mortality of the common accompaniments and consequences of influenza, bronchitis and pneumonia.

During widespread epidemics, however, the suddenness of onset, the singular rapidity of rise and fall in each locality, the speed of travel and the general basic similarity of cases and complications, have served to characterize the outbreaks themselves sufficiently to permit their recognition as true influenza. In spite of the uncertainty of diagnosis, therefore, information of considerable reliability concerning the epidemiological history of this disease is available in the writings of past centuries, such as those of Calenus of Greifswald (1579), Jacques Pons of Lyon (1596), Sydenham, (1675), Slevogt (Jena, 1712), Haygarth and Hamilton (1775), Pringle and Huxham, Massin (Strassburg, 1858) and many others. The history of influenza has been dealt with by a number of writers to whose extensive monographs the reader is referred.

Both Thompson and Leichtenstern tabulate the sequence of great influenza epidemics somewhat as follows:

1510—Epidemic, spreading from Malta to Sicily, Spain and all of Europe.

1557—Asia, Constantinople to Europe and America.

1580—First great pandemic. Origin in Orient—to Europe and entire world.

For the seventeenth century the records are very incomplete, but Leichtenstern speaks of an epidemic in North America in 1647.

Less extensive outbreaks seem to have prevailed in different parts of the world between 1709 and 1712.

Between 1729 and 1733 the disease, travelling from Russia westward, spread over Europe in two great waves, one in 1729, the other in 1732.

Another epidemic started on the shores of the Baltic in 1742.

In 1757–1758, 1761–1762, and 1767, epidemics occurred of which we have but poor geographical records.

Of the epidemic of 1742, Friedrich states that all but about one-tenth of the entire population of Germany was attacked.

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From 1781 to 1782, an epidemic supposed to have started in China spread through Siberia to Russia and thence to Europe.

Another travelled approximately the same route in 1788.

The same thing occurred between 1799 and 1803.

In 1827, there was an outbreak of Europe less extensive than most of the others.

Between 1830 and 1833 there were two or three pandemic waves, the first one supposedly originating in China.

Other outbreaks, again travelling from East to West, occurred in 1836 and in 1847. During this last named epidemic the Prussian army is said by Friedrich to have been attacked in its entire personnel.

These brief data, which bring us up to the pandemic of 1889, are condensed chiefly from Leichtenstern, who summarizes the general characteristics of influenza epidemics as follows:

1. True pandemic waves.
2. Origin in a specific part of the world. Asia (Netter); China (Pearson); Hirsch believes that some of the epidemics have probably started in North America.
3. Speed of travel over the globe.
4. Sudden mass infection.
5. Rapid burning out after several weeks in one locality.
6. Independence of season or weather.
7. Enormous morbidity with slight mortality.
8. Little influence of age, sex, or occupation on morbidity.

The degree to which these criteria may still be accepted as accurate will appear below.

When we study the records left to us by physicians who described the disease as it occurred in the early epidemics we find close coincidence with observations made during the last outbreak, not only as to the clinical data, but in regard to the chief epidemiological characteristics as well.

Huxham of Plymouth (1743) writes: "About this time a disease invaded these parts which was the most completely epidemic of any I remember to have met with; not a house was free from it. . . . . Scarce a person escaping either in town or country; old and young, strong and infirm shared the same fate." He described the disease almost exactly as we ourselves observed it at Chaumont and Baccarat

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in France in May 1918, its sudden onset, fever, chilliness, pains and rapid deferescence in about four days.

These and many other physicians recognized the essentially secondary nature of the serious pulmonary complications.

The pandemic of 1889 is supposed to have originated in the East, though records are available of the existence of an independent focus in Greenland almost synchronous with the observation of early cases in Russia and Siberia. Heyfelder saw cases in Bokhara in May 1889, and traced the enormous speed of travel of the disease north-westward into Siberia and European Russia. By October, it had reached Petrograd, by November it had entered Germany. Rapidly sweeping Westward and Southward it reached France and Austria, Italy and Spain, during this month and December. By the middle of December it had reached London and New York. Its early appearance in New York suggested to some observers the possibility that the epidemic had travelled Eastward from its original focus as well as Westward, encircling the globe, and appearing on our Atlantic coast at about the same time at which it reached the Atlantic coasts of Europe. Its course could be traced by railroad and steamship routes. The percentages of the populations attacked in each country were enormous.

To some extent the speed of travel of influenza can be seen in this epidemic to have increased in the course of the centuries, proportionately with the increased facilities for communication. Thus, in the 1872 epidemic, it took the disease eighteen days to reach Amsterdam from Leipzig, a time which corresponded to the time it took Dutch merchants to reach home from the former place (Leichtenstern).

Transmission

The suddenness of onset of influenza epidemics and the almost simultaneous affliction of a considerable percentage of a community, was perhaps the chief reason for the older beliefs that influenza may be conveyed by means other than contact; and in the past the idea that it was air borne or conveyed by dust and perhaps by insects, has had many adherents. The careful epidemiological studies which were made during the 1889 epidemic and, more recently, during the last pandemic, indicate with considerable certainty that these older

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beliefs are not tenable, and that at least the chief means of conveyance is direct and indirect contact with other human beings. The disease does not travel more rapidly than human communication, a belief formerly held. This point was studied with particular thoroughness by observers during the '89 epidemic, more especially by Parsons, Friedrich, Leichtenstern and Teissier. Numerous examples can be cited in which communities that were out of touch with the main population of a country, because of geographical isolation, were spared, or did not begin to develop cases until the reopening of routes of travel. It was noticed, by German observers particularly, that places along the railroad were the first to be affected, while the outlying country with which communication was more difficult, was several weeks late in developing the disease. Often the epidemic would reach points considerably farther away from the places of distribution if they were on main routes of travel, than it would the immediately surrounding but less accessible country districts. This was true of Kiel, one of the earliest of the German cities to be invaded. Extension to distant cities was rapid, while the country surrounding Kiel itself did not begin to report any considerable number of cases until two months later. And even as country districts were reached more slowly than were the centers through which main routes of travel passed, so also did the epidemics percolate through them more slowly and remain in them for relatively longer periods, proportionate probably to the greater dispersion of the population and the lessened opportunities for contact. Thus, Parsons noted that in some of the rural communities of England the epidemic trailed along for some four months during which it swept over the crowded industrial districts with the sudden blazing and subsidence of burning straw.

In large cities the epidemic has usually burnt itself out in a relatively short time. Leichtenstern who has carefully gone over most of the reported data of the 1889 epidemic, generalized in the following way: The first cases are usually followed within two weeks by true epidemic prevalence. After that a very rapid extension occurs which is at its peak in three weeks, and subsides almost completely within the following fourteen to twenty-one days. In Munich, a city which was very carefully studied, the epidemic began about the first of December and from December 27 to January 4 there were 1100 to 1600 cases daily.

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By the middle of February the epidemic was almost over. Abbott's careful study of the epidemic in Massachusetts shows that about seven to eight weeks covered the first epidemic period. It reached its peak throughout the State of Massachusetts during the week of January 4 to 11, 1890, and was practically over by February 10. During this brief period over 800,000 people were attacked, that is about 40 per cent of the population. In London the epidemic appeared first in December, 1889, and during January attained a death rate of 28.1 per 1000. During February it rapidly declined and ended during March. It is interesting to note that in some of the large industrial cities of England the epidemic was three to four weeks later than in London, the death rate in London in January not being equalled by most of these towns until February.

During this epidemic also there were a number of more or less isolated communities which were spared. Thus, there was no influenza on the Isle of Man and in the Bahamas. On the Santis Mountain which is about 7000 feet high there was no contact between the inhabitants of the observatory and the valley and there were no cases of influenza during the epidemic. On the Island of Borkum, Leichtenstern states, there was a period of freezing weather in late December and early January, during which the Island was completely isolated. The first cases did not appear until three days after arrival of the first ship. He adds that similar conditions prevailed at Vladivostok and Sachalin, places in which the disease did not appear until the spring of 1890 when the thaws made the resumption of travel possible. Friedrich cites definite data to show that the disease was brought from Danzig to Hadersleben by ship. In France the same thing was observed, and there seems to be very little doubt about the fact that human communication lies at the bottom of transmission from place to place.

During the pandemic of 1918 the same thing was probably true, but because of the active transportation of large masses of men incident to the state of war, the routes of transmission were so completely interwoven that it has not been easy to unravel them. Whether the epidemic spread from France to the United States as suggested by MacNeal, whether it travelled the other way, of whether it began in several places at the same time, are questions that prob-

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ably will not be settled until more complete data have been collected by epidemiologists throughout the entire world and have been scrutinized by men as well versed in epidemiological analyses as Frost and others. There is, however, a very interesting example of travel by ship during this epidemic, reported by Colonel Delaney of the American army from England which we cite from MacNeal's paper. On August 26 and 27, a British vessel, the Mantua, with influenza on board, stopped at Sierra Leone for consultation with two British ships, the Chepstow Castle and the Tahiti, the Chepstow Castle acting as a transport for New Zealand troops, the Tahiti carrying navy ratings from East Africa. Influenza appeared on board both of these ships forty-eight hours after this call, with sixty-eight deaths on the Tahiti and thirty-eight deaths on the Chepstow Castle before arrival in port. New Zealand and East Africa had not been reached by the epidemic when these boats started. But on October 23 the steamer Mozambique arrived at Lisbon from Cape Town with 200 deaths during the voyage, and reported an epidemic of influenza at Cape Town at the time it left. Writing in the Lancet (1918, ii, 455) the Medical Officer of Health in India states as his opinion that the epidemic appeared in India with such terrible consequences in the summer of 1918 was not endemic, but was introduced by shipping.

The opinion of direct and indirect transmission from man to man is also well supported by a detailed study of the epidemiology of individual outbreaks. In our own experience with local epidemics such as those at Chaumont, Baccarat and other places, the suddenness with which the malady attacked large numbers of people at almost one and the same time, caused us at first to be exceedingly skeptical of accepting transmission by contact as the only means of conveyance. We considered food and insect transmission as possibilities, and tried our best to find grounds for involving such agencies. But, in every case we were forced to return to the conclusion that direct and indirect contact between men came nearest to doing justice to all observed facts.

An interesting small hospital outbreak has been described by Foster and Cookson which clearly exemplifies contact infection. A surgical ward, free from medical illness for some time before, on June 6 received an influenza convalescent suffering from a surgical lesion.

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This man spit a great deal, and was dirty in his habits. On June 9 the man in the bed next to him developed influenza and the blood culture of this case contained influenza bacilli (!). On the same day the man on the other side of the original case developed a temperature of 104° with symptoms of influenza but negative bacteriological findings. The disease then travelled from bed to bed, along the line of beds on that side of the ward, until it stopped at both ends when it came to empty beds. Another influenza case was admitted to the other side of the ward, and from it the neighboring bed was infected. But on this side the disease remained limited to these two because the adjoining beds were screened from them by elaborate surgical traction arrangements. The diagram of this little epidemic is sufficiently instructive to warrant reproduction.

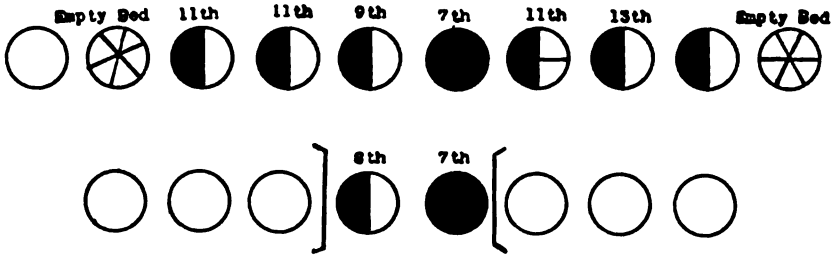

DIAGRAM A
(Taken from article by Foster and Cookson, Lancet, 1918, 2, 585)

Bearing upon the same point are certain data which we take from a report of Stanley concerning an epidemic in the St. Quentin Prison, California. Stanley definitely traced the origin of this epidemic to the admission of a prisoner from the county jail in Los Angeles. The man had been sick before he came in with symptoms described accurately as influenza. On his entrance to the prison he mingled with 1900 men congregated in the ward, and ate in the general mess with them. At night he was locked in the receiving room with 20 other prisoners. On the day following this he had an apparent relapse of his influenza, and was admitted to the hospital with a temperature of 101°, chilliness, pains in the back and bones. Following this an epidemic of unusual severity started in the hospital, reaching its height ten days after the new prisoner had been admitted. On the tenth and eleventh day after the arrival of this man, 1900 or one-half

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of the entire prison population were ill. The ordinary daily sick-call of the prison was about 150 to 200, whereas, on these days 700 to 750 appeared at the doctor's office. Stanley also noticed that during the period of the epidemic, which lasted a little over a month, the largest number of cases occurred on the Tuesdays and Wednesdays of the second and third weeks, and explains this by the fact that on every Sunday morning two moving picture shows were given, one at 8:00 a.m. and the other at 10:00 a.m., respectively, in a poorly ventilated room. Almost the entire 1900 sick men had attended these shows. Stanley places the incubation period, accordingly, at about thirty-six to sixty hours. (This corresponds roughly to our own observations in which several cases in which the time of contact could be reliably ascertained showed incubation periods of about forty-eight hours.) About six months after the first epidemic, a second one broke out in the prison, again introduced by a new arrival from Los Angeles. This prisoner became ill on the day after admission, showing the characteristic symptoms. Before becoming ill, however he had spent one night in the receiving ward, and had taken his meals with the 1900 other prisoners. This epidemic went through the prison more slowly, and there were fewer cases than in the first epidemic. How much this may have been due to immunity of the remaining prisoners, we will discuss further below. In part, the lessened morbidity may have depended upon the very rigid precautions which were taken, the prevention of assembly of prisoners in large numbers, and other sanitary and hygienic measures which were enforced. A third epidemic occurred a month after the second, but lasted only about nine days. During this outbreak a number of interesting additional observations were made. A prisoner, "A," reached the St. Quentin Prison by train on November 21 from Colusa County where an epidemic was then raging. He felt badly the next day, but did not report to the doctor and was put in a room with twelve other prisoners. Though feeling sick he attended the moving picture show on Sunday, on the evening of which day he was removed to the hospital. In the receiving room "B" and "C" slept in adjoining beds. "A" sneezed and coughed into "B's" face at about 4:00 p.m. Sunday afternoon. At 9 a.m. on Tuesday, "B" began to have chills and fever. "C" was also closely associated with "A" and "B," and

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became sick on the same day that "B" did. Stanley made a careful study of the distribution of cases in the auditorium where the moving picture shows were held, and found that there were approximately five centers about which the infected men sat; the largest one was in the middle of the room, and in each corner there was a separate focus. Nobody was infected in the orchestra pit, where there were 10 men. The orchestra sat 9 feet in front of the first row of auditorium seats. There was a women's department of this prison which had, at the time, 30 inmates. This is a separate building, and absolutely without contact with the men. None of these women had influenza during the three epidemics. Stanley's studies seem to indicate not only that contact is the method by which the disease is conveyed, but also, that fairly close contact is necessary; and his results show that complete isolation, when it can be rigidly carried out, as in closed institutions, is effective.

Jordan has carefully studied three groups in Chicago, namely, the Students' Army Training Corps, the high and elementary schools of the University of Chicago, and the Chicago Telephone Company. In the Students' Army Training Corps there were two sections, A and B. They lived under the same conditions, but most of the boys in section B came from small towns in Illinois, while most of the boys in section A came from Chicago itself. For some reason or other, section A was closely supervised, with prompt removal of those who were slightly ill, whereas in section B these precautions were not carried out to the same degree, and 3 of these boys were ill on arrival in Chicago. Section A had 26 cases, whereas section B had 92 cases within six days. In the elementary school group Jordan's analyses show definitely that there was a sharp rise about November 30 following the Thanksgiving recess from Wednesday until Monday, during the family gatherings, etc., formed an opportunity for infection, and at which none of the precautions were probably taken which were habitual at this time in the routine of school attendance.

Onset of epidemics of influenza

In regard to the suddenness with which the disease attacks large numbers of people in one and the same place, at almost the same time, recent records thoroughly confirm the observations of the past. In

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our own experience during the first outbreak at Chaumont, 54 men of a single company were attacked within 11 days, out of a total strength of 172, and no less than 41 of these 54 men were taken ill within two days, May 15 and May 16. Thus:

On May 13 there were 3 cases
On May 14 there were 3 cases
On May 15 there were 19 cases
On May 16 there were 22 cases
On May 17 there were 3 cases

From then on until May 23 when the disease stopped in this unit, there were only 4 additional cases.

In another place we saw as many as 73 cases, developing in the same day in a single infantry company. Wirgman writing in 1918 speaks of an outbreak at a camp of 560 men in which almost the same sort of thing happened. In a report on an epidemic in Rest Camp no. 4, Base Section no. 2, American Expeditionary Forces, near Bordeaux, Ward reports that in one camp with a strength of 3400 men there were 82 cases within two days, and in a camp of 180 men, there were 20 cases on one day.

Therefore, although the total morbidity and mortality statistics of any influenza epidemic compiled for a large territory usually covers periods of months, yet when the individual local outbreaks are studied, it is found that in any given locality the disease burns itself out within an extremely short time, then passing on to the next.

The speed of travel in influenza may to a certain extent be explained by the almost universal susceptibility of the race to this disease, and to the fact that a large percentage of the cases (especially the early ones) are extremely mild. The percentage of the recognized sick, who seek medical advice does not represent the total number of the afflicted since a very large number of people during such epidemics suffer from perhaps nothing more than headache, general malaise, and trifling fever of short duration. In a military unit which we had occasion to study, we were able to determine that although the number who came to sick call and needed hospital care was very large, there were, in addition to this, a considerable number of men who were unquestionably infected, but who were so slightly ill that they continued on duty. It is not at all unlikely that during epidemics

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(and this is a thought also expressed in connection with the '89 epidemic by Leichtenstern) a large number of people are well enough to travel and to go about their daily business, although in the active stages of mild attacks and, therefore, capable of transmitting the infection. In most other infectious diseases the majority of the sick are immobilized, at least for a time, and transmission by travel is thus prevented in the majority of cases.

The free circulation of large numbers of people who represent unrecognized, potential sources of infection, and their unrestricted intercourse with others in all the activities of business life, family relations and travel, coupled with an almost universal susceptibility of the population at times preceding epidemics, would go far to explain both the tempestuous beginnings and the rapidity of extension.

Moreover, as regards the suddenness with which a large number of people are simultaneously afflicted, a feature which has kept alive some skepticism regarding the contact method of infection, such statements should be made with qualifications. Parsons, in his studies of the epidemic in England in 1889, 1890 and 1891, calls attention to the fact that the rapidity of onset in influenza is not essentially different from that which formerly prevailed in smallpox before the day of universal vaccination. It is probable that, when the disease strikes a community, its explosiveness is actually much less marked than it appears to be from morbidity statistics; and, as Leichtenstern and others have noted, it was usual during the '89 epidemics, that outbreaks were clearly recognized as possessing true epidemic dimensions not earlier than two weeks or more after the first cases had actually occurred, a fact not generally brought out until subsequent studies have been made on the basis of completely available data. Parsons, furthermore, has found evidence which indicates that in many cases in which the onset of a local outbreak was particularly explosive, this could be traced to the assemblage of large crowds in meetings or conventions, during the days just preceding the epidemic. In the small town of St. Davids the outbreak followed a large public meeting. In Eccleshall an epidemic followed two or three days after an Odd Fellows picnic. In Kington in 1891 the outbreak was associated with the May fairs.

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During the last pandemic this phenomenon of explosive onset was noticed chiefly in connection with military units where association in closely related groups was one of the exigencies of military life. It was quite evident in at least one of the epidemics which we had occasion to study that the characteristics of the outbreak in the military groups differed in this respect considerably from those prevailing at the same time among the surrounding population. Thus, at Chaumont, while the outbreak among the Marines and in some of the other military units took the form of the steep peak which we have described above, the disease extended more gradually and trailed along more irregularly and for a longer time among the clerical force who were scattered in many different billets and offices. And this was still more noticeable as regards the civilian inhabitants of the town, among whom the percentage morbidity was much lower and was scattered much more widely both as to time and place.

Moreover, even in military units like the Marine Company mentioned above, where the explosiveness seemed extreme and "mysterious," simple analysis removes much of the mystery. If we take this little outbreak as an example we see that 6 recognized cases had occurred on the two days preceding the sudden appearance of 19 cases on a single day. These 6 had been in the incubation stage for at least twenty-four and forty-eight hours previously, and probably did not represent the total of infected men; for it is more than likely that there were a number of others who were not sufficiently ill to report at sick call. If we consider, therefore, that at least 6 and probably more men circulated freely among the remaining 166, and ate and slept in close association with them, we find that the apparent suddenness of the rise in morbidity on the third and fourth days of the outbreak is not out of keeping with the assumption of contact infection. The impression conveyed by the steep graphs of such outbreaks is, therefore, apt to be misleading.

Secondary outbreaks

In the wake of almost all influenza epidemics there have followed secondary outbreaks which are often spoken of as "waves." This has apparently been the case in all the large epidemics of which we

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have definite knowledge. Leichtenstern has commented upon it extensively in connection with his study of the '89 epidemic.

After the epidemic of 1729 to 1730 there were secondary waves in 1732 and 1733.

The 1789–1791 outbreak did not become entirely quiescent until a definite secondary wave had followed in 1792.

The 1798 epidemic was followed by one in 1800.

After the outbreak of 1836 to 1837, others followed in 1838 and 1841.

The 1847 to 1848 epidemic was followed by another within a year, and conditions in the world did not return to normal until 1851.

Parsons writing for the British Isles states that there were three definite waves from 1889 to 1892. The first began in the winter of 1889 to 1890. Another occurred in the spring of 1891, a third in the winter of 1891 to 1892. The following chart (page 282) taken from the article by Frost and tabulated by months, from 1887 to 1916 for Massachusetts, from death rates per 100,000 from influenza and from all forms of pneumonia, shows that here, too, the epidemic of 1889 to 1892 developed in three distinct waves, the first one coming to a head in January, 1890, the second in April and May, 1891, and the third in January, 1892. The same thing occurred all over the world, and tabulations of individual cities like New York, New Orleans, Chicago, as well as studies in other parts of the world indicate a similar wave-like repetition.

Brownlee has attempted to find a law of periodicity for the large intervals between pandemics, and the intervals between the separate waves of each outbreak. Since statistical studies of pure uncomplicated influenza alone would for many reasons hardly be accurate enough as a basis for such calculations, Brownlee, Frost and other epidemiologists have reduced the factor of error by making their calculations both from influenza statistics and from total reports of all pneumonias, comparing these with the pneumonia incidence and mortality of interepidemic years. Brownlee has studies the weekly number of deaths for London from 1870 on. He finds the period between influenza outbreaks, between 1889 and 1896, to be about thirty-three weeks. There is no such periodicity in regard to bronchitis and pneumonia in the absence of influenza, and Brownlee concludes that if such periodicity appears after the return of influenza,

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TABLE 1

Death rates per 100,000 of population from pneumonia (all forms) and from influenza in Massachusetts, 1887–1916, inclusive

PNEUMONIA

YEAR	TOTAL PER YEAR	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER
1887	138.8	19.5	16.7	1.9	22.6	16.1	7.7	5.5	4.1	5.6	9.0	14.8	15.3
1888	172.7	24.7	25.1	26.4	21.3	16.4	8.0	5.5	4.0	6.2	11.4	9.8	13.9
1889	156.6	17.9	16.3	21.1	19.8	14.9	7.5	5.3	5.2	5.4	10.6	13.2	19.3
1890	180.0	47.8	17.7	17.6	20.1	12.7	8.5	6.2	4.8	5.0	9.4	11.8	18.3
1891	188.5	20.6	16.4	20.6	25.1	23.9	10.1	5.9	4.0	4.0	7.7	13.8	36.4
1892	213.0	61.5	25.2	23.1	21.4	17.0	8.3	5.4	4.2	6.8	8.5	12.5	19.0
1893	225.8	27.3	25.4	28.6	33.1	27.3	11.1	8.0	5.0	6.1	9.8	14.3	31.9
1894	166.0	32.8	19.9	22.7	18.5	14.0	8.5	5.1	5.1	6.8	8.2	11.3	13.6
1895	184.1	19.1	34.4	30.8	20.9	14.4	7.6	5.6	5.3	4.7	10.5	13.4	17.3
1896	182.0	19.5	20.7	24.9	25.9	18.7	10.3	7.6	4.5	7.6	10.7	12.7	18.8
1897	181.6	21.1	24.9	31.5	19.7	15.2	10.2	7.0	4.5	6.0	11.7	13.1	16.9
1898	156.0	18.8	17.1	18.5	18.7	15.7	6.6	6.0	4.8	5.6	10.6	12.8	21.0
1899	181.3	37.5	25.8	20.6	18.4	14.0	8.9	5.0	4.8	5.8	8.2	13.2	19.0
1900	188.3	22.7	21.1	42.0	30.5	17.6	8.7	5.3	4.3	5.3	6.2	9.9	14.7
1901	167.7	22.6	26.6	26.2	19.9	13.9	7.7	3.4	3.4	5.7	9.1	14.2	15.1
1902	158.9	15.7	18.9	19.9	16.8	15.5	8.0	6.2	5.3	5.7	11.8	14.5	20.6
1903	172.5	25.2	25.8	25.4	18.1	16.8	8.2	7.0	4.5	4.6	7.7	13.3	18.9
1904	172.1	22.6	22.7	24.1	21.2	14.2	6.7	5.9	4.4	6.5	9.4	15.0	19.5
1905	178.3	24.7	27.7	23.6	17.1	15.5	8.5	5.4	4.8	6.2	8.9	15.8	20.0
1906	174.1	22.5	21.9	24.1	21.7	14.9	5.1	6.2	5.0	6.0	9.4	13.8	21.0
1907	180.4	25.5	24.4	23.4	18.3	14.3	9.5	5.1	5.1	7.1	9.3	12.7	26.9
1908	165.8	26.6	22.2	21.1	19.4	13.5	6.6	4.9	5.8	6.4	9.2	12.4	17.6
1909	170.3	22.1	20.0	26.1	20.1	16.0	9.7	5.1	5.0	5.4	8.9	13.6	18.3
1910	197.6	24.1	20.7	27.5	23.3	16.9	9.7	7.3	6.3	9.1	12.3	17.0	23.6
1911	174.4	22.6	27.1	23.9	20.2	16.9	7.2	6.7	6.1	6.7	9.0	11.8	16.2
1912	152.0	19.8	20.2	21.2	16.4	13.3	6.2	5.0	4.1	5.8	9.5	10.5	19.9
1913	172.2	23.5	22.8	24.9	19.3	17.1	10.7	6.2	5.4	6.7	8.3	10.4	16.8
1914	166.0	22.9	20.1	23.2	20.4	15.2	8.2	5.1	5.5	6.0	10.1	12.6	16.8
1915	176.0	17.8	19.3	28.5	27.7	13.6	6.6	7.1	5.8	6.0	8.8	9.8	22.1
1916	176.6	35.6	25.5	23.0	17.3	14.0	7.4	5.3	4.1	5.9	7.6	12.8	18.3

Taken from Frost, Public Health Reports, U. S. Public Health Service, xxxiv, no. 33, p. 4.

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it must be definitely associated with this disease. From 1876 to 1889 the thirty-three-week recurrence was missed in regard to bronchitis and pneumonia, but in the years 1889 to 1896 it was marked. Comparing the monthly statistics of Glasgow, Aberdeen and Massachusetts he finds that there is nothing which differentiates them in principle from the phenomenon in London. Stallybrass supports these calculations of Brownlee, and speaks of a minor cycle of thirty-three weeks within the pandemic periods and major one of about ten years between pandemics. We are not ourselves in a position to comment upon these findings.

Pearl's paper "Influenza Studies" published in 1919, incidental to an analysis of the mortality curves of 40 American cities takes up the time manifestations as they occur in local outbreaks. He finds that such curves are of two main types, one showing a single well-defined peak, others showing a first high peak followed by one or more smaller ones. The latter type was of the usual form. A further analysis of these curves showed that there was a definite tendency for the "two-peak" curves to fall into two groups. About one-third of them had their second mortality maximum about eight weeks after the first peak. The remaining two-thirds had their second mortality maximum on an average of about thirteen weeks after the first peak. Those in which there was a third peak had their second one about 7.1 weeks after the first, and the third on an average of about 13.1 after the second. Pearl believes that according to this, the cycle in such successive waves appears to be nearer a multiple of seven rather than of ten weeks.

A great many statisticians, far more capable of judging of these matters than ourselves, are now engaged in a study of the cyclic phenomena and no doubt will publish their conclusions in time. Meanwhile, we wish merely to mention the matter as one of the important problems of influenza study undertaken at the present moment.[2]

The second and third waves of epidemics have been marked by a number of characteristics which are of important significance. Both

[2] For a more extensive discussion of the problem of periodicity and its probable significance, we may refer the reader to the extensive monograph of Warren T. Vaughan, published since this paper was first prepared.

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Parsons and Frost find that in the epidemic of thirty years ago the mortality was progressively higher during the 1891 to 1892 waves than during the original outbreak in 1889. Leichtenstern states that although the mortality, which of course is largely due to secondary infection, is greater during the secondary waves, the general morbidity of influenza is smaller. This corresponds with the observations of Wutztorff who analyzed the epidemic in Germany with considerable care. Wutztorff admits that it was extremely difficult to obtain accurate estimates of influenza morbidity during the later waves of the pandemic. But, although he finds that in some towns, especially in North Germany, the 1891 to 1892 wave was almost as extensive as that of 1889 to 1890 had been in other places, in general the morbidity in Germany was much lower. To some extent his conclusions are derived from indirect evidence such as, for instance, the fact that the hospitals in the various cities were not taxed to overflowing during these later waves as during the first, massive infection of the entire personnel of many industries and of railroads did not take place to the same extent, and the statistics of the government physicians stationed in various parts of Germany showed that a much lower percentage of the population sought medical advice. As a rule, from 6 to 7 per cent of the population sought treatment during the first epidemic, whereas only from 2 to 3 per cent reported during the later waves. It would be impossible to reproduce the extensive statistical and other evidence brought forth by Wutztorff in support of his contention, but we may assume as probably correct that in the later waves morbidity is usually lower and the percentage mortality somewhat higher than during the first.

Noticeable also is the fact that secondary epidemics do not travel with the same speed and to the same geographical extent as does the first wave. There is generally slower progress, a greater scattering of cases, and a somewhat more prolonged period of prevalence in the subsequent waves; and, judging from the careful study of mortality statistics in years following the pandemics, it is more than likely that after the so-called third wave there may be a succession of what we may term gradually diminishing "ripples" which finally fade out, in the course of some years, into practical quiescence. Leichtenstern seems to believe also that the secondary outbreaks are characterized

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by the fact that they originate in many different foci simultaneously instead of proceeding (as he and some others assume that first waves do) from a single focus. Netter holds the same opinion. He says of the secondary waves of the 1889 pandemic that "they have appeared in separate, synchronous or successive explosions, and we have not been able to trace any connection between various reappearances in different places, as this was possible in 1889. There seems to have been an independent reawakening of the epidemic in different localities." In a general way this is probably true, but we will see, when we come to discuss the course of the first wave of the last pandemic that some of the most experienced epidemiologists are reluctant to assume that this outbreak proceeded from any single world focus.

The origin of influenza epidemics with particular reference to the origin and course of the last pandemic outbreak (1918)

In a recent address to the Congress of American Physicians and Surgeons, Flexner made the interesting suggestion that perhaps the most effective method of forestalling epidemics in the future would be to search out and attempt to circumscribe the endemic foci in which the cinders of disease are constantly smouldering during the interepidemic periods. This method of procedure has been effectually initiated in the case of yellow fever, and would seem to be an eminently logical one for application to other insect borne diseases. It might also be successfully applied in plague and conditions like it in which interepidemic propagation is carried on largely in animals. In regard to other diseases the promise of even partial success would be directly dependent upon the question as to whether the particular condition is kept alive, between outbreaks in special centers in the world or whether the foci are widely scattered in all populations in the persons of carriers, constantly increasing in number along the trail of sporadic cases, as in typhoid and the paratyphoid fevers, etc.

The idea is an extremely important one since any step in the direction of interepidemic control of foci, if attended by even a slight degree of partial success, would accomplish more at smaller expense than the most energetic attempts at suppression after epidemics have started. Moreover, the splendid efforts which are being made, at the present time, to internationalize public health activities pro-

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vide an opportunity for possible accomplishment of such a project which has never before been within reach.

In the case of no disease should this proposal be more seriously considered than in that of influenza, since no other condition attains a comparable degree of destructiveness, none travels so sweepingly over the whole world, and in none other are we so totally helpless to obstruct its progress. It is, therefore, of great importance to determine, if possible, whether influenza epidemics have truly emanated from definite endemic foci, or whether they have started in various parts of the world at times when conditions such as the declining resistance-values of populations, or some other unknown factors have created epidemic possibilities.

In the tabulation cited from Leichtenstern and others we have indicated that many of the epidemics of the past were supposed to have emanated from the East. Flexner, unquestionably following similar reports, assumes that the region on the border between Russia and Turkestan may possibly be regarded as one of the important endemic foci. At any rate, the reports of earlier writers have again and again referred to China, the Caucasus, Eastern Siberia and Turkestan as furnishing the initial blaze which then spread, Westward and Eastward, to encircle the world. The possibility of the regional delimitation of influenza foci is, therefore, more than a surmise and should be examined with care, especially as light has been thrown upon it by the more exact epidemiological investigations of the last two great outbreaks.

The beginnings of the outbreak of 1889 seemed again to be traceable to the East. The reports of Heyfelder and others to this effect have been mentioned in preceding sections, but there seems to be evidence that the disease appeared in Greenland and in Northern Canada at a time so early in this epidemic that it cannot be accounted for by Northwesterly spread from the South Eastern continental sources.

It appears also from the studies of statisticians that influenza remained widely dispersed throughout the world for many years after this epidemic had subsided; so long in fact that it seems very unlikely that we can ever speak of well defined endemic potential sources of origin except in a relative way. Indeed, the permanently increased influenza incidence in places like China, if considered from this point

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of view, may be due to nothing more than to defective conditions of hygiene and sanitation coupled with greater crowding. Prof. Raymond Pearl in commenting upon the probability that the 1918 epidemic will be followed by a long period of increased influenza morbidity, makes the statement that the curve of mortality from influenza in England and Wales was higher in 1907, seventeen years after the 1890 epidemic, than it had been in any of the forty years immediately preceding this outbreak. He adds that a similarly slow decline of mortality followed the epidemic of 1848.

It is likely, therefore, that for many years after pandemic waves have subsided, perhaps throughout the interepidemic periods, the virus remains freely scattered among the populations of the world, ready to flare up in renewed mass infections when gradually declining incidence over a period of years has brought about a reduction of community resistance; and at such times it would be most likely that the points of least resistance, (and, therefore, the most frequent sources of widespread epidemics) should be located in the most crowded and least sanitated communities.

It is too soon to come to any definite conclusions regarding the origins of the 1918 epidemic. Epidemiological methods have developed considerably since the last preceding outbreak, and no final judgment can be rendered until properly qualified epidemiologists have had the opportunity of gathering and studying all available evidence. Like others who cannot pretend to anything more than a superficial knowledge of statistical methods, we must be content to await these analyses. Meanwhile, however, it will be of interest to discuss available information on this problem in a tentative way.

As in the case of previous epidemics this one is supposed by some writers to have originated in the East. McNalty, in the article referred to above, states that in March, 1918, the disease was prevalent in China, and that, in the same month and in April, the Japanese navy, perhaps infected in Chinese ports, suffered from a serious outbreak. This is particularly interesting to us, since we remember distinctly hearing of a curious, mild febrile disease reported among Chinese labor troops on the coast of France early in the spring of 1918, about which we have never been able to obtain definite clinical or epidemiological information. These facts would incline one again to suspect

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the existence of a single source of origin. More searching inquiry into the beginnings of this pandemic, however, throws considerable doubt upon such a simple solution of the problem. Frost who has given particular attention to the study of general mortality rates from influenza and pneumonia has, among other things, analyzed these rates for a number of American cities during the years 1910 to 1918. He finds that in December, 1915, and January, 1916, there occurred in New York and Cleveland a sudden and considerable rise in the mortality rates from these diseases. In January, 1916, he states, influenza was reported to be epidemic in twenty-two states of the Union (U. S. Public Health Reports, January 7, 1916)—epidemics which "were so mild that they attracted little attention at the time and were generally forgotten." Even though we make all due allowance for the looseness of the clinical term "influenza" by which many of these cases were reported, these facts are significant in pointing to unusual conditions in regard to the prevalence of diseases of this type some years before the pandemic gathered sufficient velocity to be seriously regarded.

During the winter of 1917, when the army concentration camps were being filled in the United States, pneumonia occurred in many of them in an epidemic form, which, however, was in most cases unassociated with any influenzal element. In a few cases, however, mild influenza-like outbreaks preceded or accompanied these pneumonia epidemics. When recently we described influenza as we first saw it at Chaumont, France, in May, 1918, we were told by Dr. George Draper that he had seen a number of exactly similar cases at Fort Riley in the winter of 1917. For Europe, too, there is evidence that indicates that influenza was endemic during the years preceding the great outbreak and that a number of minor epidemic explosions had occurred in the years just preceding 1918. MacNeal who has investigated military reports, particularly, states that small epidemics occurred in the British Army in 1916 and 1917. A chart constructed by him, from the American Expeditionary Force reports, shows that a considerable rise in reported influenza cases took place in November and December, 1917, and in January, 1918, gradually declining toward spring. MacNeal, compiling the data available in the office of the chief surgeon, American Expeditionary Forces, states that the

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influenza morbidity reported per 100,000 for succeeding months in 1917, were as follows:

July	321
August	438
September	404
October	1050
November	1980
December	2480

Robertson who studied many of the secondary pneumonias which came to autopsy at this time found an unusual type of lobular pneumonia in which Pfeiffer bacilli were frequently found. In many of these cases the organisms could be obtained from the nasal sinuses and antra. Similar findings were reported by British bacteriologists (Hammond, Rolland and Shore, Lancet, 1917, ii, 41, and Hallows, Eyre and French, Lancet, 1917, ii, 377) who studied the cases that occurred in the British Armies both at home and in France. We have also found in reports by Austrian physicians reference to outbreaks of typical influenza on the Austro-Russian front early in 1917.

There seems little doubt, therefore, that for some years before the pandemic of 1918 influenza was endemic in many parts both of Europe and of America. As early as 1915–1916, Frost finds evidence of limited epidemic outbreaks in the United States. During the winter immediately preceding the true beginning of the pandemic small outbreaks occurred among the allied troops in France, the British troops in England, and probably among American troops gathered in home concentration camps as well. MacNeal in a summary of the conditions prevailing among American troops in France concludes that epidemic influenza in that country originated from the endemic foci there existing and that the disease was probably carried from Europe to the United States by shipping. The former assumption, namely, that the epidemic occurrence of the disease may have been due to the fact that an enormous and concentrated newly introduced material of susceptibles may have been lighted into flame after arrival in France at the numerous endemic "smoulders," may well be correct. The latter, however, concerning the transportation of the disease from Europe to America may justly be questioned. For, in the first place, Frost's studies have shown that prepandemic outbreaks were quite

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as frequent in the United States as in Europe during 1915 and 1916, and, though we have no definite proof of this there is reason to believe that influenza was prevalent in concentration camps during 1917.

Moreover, when the disease was beginning to gather headway in the rise of the first wave in 1918, definite outbreaks in the United States seem to have preceded those in Europe. The earliest reports from Europe, so far available. seem to place the beginnings of the epidemic somewhere in April, 1918. Yet in March there was a very definite though mild epidemic at Oglethorpe, Georgia, which was reported by Vaughan and Palmer and has been referred to above. Similar epidemics seem to have occurred in Chicago in March, and the epidemic which occurred in St. Questin Prison in April was, according to Stanley, started by the reception of an infected prisoner from Los Angeles, where the disease must have been prevalent at that time. It was at about this time that the writer heard of the curious disease among French Indo-Chinese troops on the Coast of France, a matter that is mentioned only in order that some one who may have access to suitable records, may on reading this, look for evidence more definite than rumor. The first concise reports in Europe seem to have come from Spain in May. The course of the epidemic after this time is extremely difficult to follow owing to the concentration of large bodies of men under active military conditions and the transportation of troops from one country to another. Within a month it had spread to Portugal, France, Holland, Germany, Austria, Hungary, Russia, Switzerland, Norway and Denmark. What the exact order of appearance from one country to another may have been, we are not in a position to say. Nor are we sure that it will ever be possible to trace this even when all records are available. Certain it is that outbreaks soon became almost simultaneous in many different parts of the continent. By June it had appeared in the Philippines and India. (In India too there had been mild outbreaks earlier in 1918 in the Province of Tana, presidency of Bombay, but a report from Major White to the government of India indicates that a fresh introduction of the disease seems to have taken place in May when cases were reported in Bombay, subsequent to the arrival of a transport from Mesopotamia.) A little later it spread through South Africa and in July appeared in Egypt whither it is said to have been brought from Malta and Salonica.

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It seems fairly definite, therefore, that the last pandemic cannot be said to have started in any single endemic focus. It appears to have grown from roots that can be traced back to 1915 and 1916 at least, and according to studies such as those of Pearl it seems quite possible that none of the crowded communities of the world had become entirely freed from the disease after the 1889 outbreak. It is not impossible, however, that the last pandemic may have been epidemiologically abnormal owing to the unusual conditions incident to war, the creation of great foci of respiratory transmission in the camps and the transportation of infected men in large numbers under conditions eminently suitable for the dissemination of disease. Moreover, there was a constant rearrangement of human association, a constant addition of fuel to the centers of epidemic prevalence, in the form of recruits sent to camps, American susceptibles sent to France and transport-infected individuals unloaded into dense populations in both directions between Europe, America and other continents. It is a suggestion at least worth considering whether this pandemic might not have been delayed in its advent, or perhaps limited in its scope had there not been a state of war throughout the world.

Thus, although the last epidemic unquestionably started from a number of different sources, and although it will probably take many years before the respiratory disease rates have returned to normal interepidemic levels, it will still be eminently worth while to study the problem as to whether there are localities in the East in which, owing to particularly unfavorable sanitary conditions or other factors the disease is more prevalent than in the rest of the world, and to begin prophylactic epidemiology in these places.

Course of the pandemic of 1918

Like the 1889 epidemic the last pandemic appeared in successive waves. It is a little difficult at the present time to say exactly when we should consider the first wave to have started. In the United States the sharp rise of influenza mentioned by Frost as occurring in 1915 to 1916 might be considered a preliminary wave.

According to the report of the surgeon general of the United States for 1918, it is not impossible that a definite influenza epidemic existed in the United States in 1917. During this year he states that approx-

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imately 4572 cases of influenza were reported in the United States army, but no separate tabulations by camps were made at that time for the Annual Report. Practically none of the 1917 cases were reported as associated with pneumonia, but in analyzing his tabulations the surgeon general concludes that in a large number of the camps in the United States in 1917 there were epidemics of influenza which began in October, extending through November, usually decreasing in December, with further decrease in January, decided decrease in February, and a subsequent increase either in March or April. Furthermore, a number of cases of the disease were reported during the summer months together with a considerable number of pneumonias. The surgeon general also notes that from the very beginning of 1918 there was a respiratory disease rate above normal.

A similar early appearance of the disease in 1917 in minor outbreaks in the British army and in France generally has been alluded to above in the attempt to analyze the possible origins of the last pandemic. When the history of the epidemic is finally written by competent statisticians on the basis of accurate data it may well be found that it did not appear in its maximum force in a first overwhelming wave, but that there was a gradual sequence of progressively increasing wavelets which led up to the main outbreak, analogous in a reverse way to the gradual decline in waves as the epidemic subsided; and, although, this seems quite different from the story of past epidemics, it is not impossible that this is due only to the fact that in earlier epidemics the preliminary outbreaks were insufficiently recognized and studied. Thus, we have already noted above that Heyfelder speaks of the similarity of his early cases in 1889 to cases of so-called dengue fever which occurred in Constantinople in 1888.

However this may be, the first generally recognized wave of the last pandemic seems to have occurred in the spring of 1918. This probably began in March, April and May, at which time there were reports emanating from China and Japan almost simultaneous with similar reports from Camp Oglethorpe in America, followed rapidly by outbreaks in France among civilians and American, French and British troops. It seems at that time to have been prevalent in American cities, especially New York and Chicago, appearing in Spain in the latter part of May and early June, reaching England in

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June and July. According to the information we can gather from the German medical press, the disease must have been prevalent in Germany and Austria prior to July, 1918. At probably the same time it reached South Africa. According to a report of Major Norman White, high sanitary commissioner of India, the disease began epidemically at Bombay in June, 1918, but the first sporadic cases seem to have occurred in May on a troop ship coming from Mesopotamia which indicates that the disease must have been in Mesopotamia previous to that. According to Findlay the first cases in Egypt occurred at Port Said in the middle of July, introduced by shipping from Malta and Salonica.

According to Frost the rise in the Central and Western cities of the United States occurred in April when the pneumonia reported showed an unmistakable departure from the normal; and the increased mortality extended into May. But Frost notes that on the Atlantic seaboard, especially in New York there was a definite increase generally during the January, February and March, preceding.

It seems definite then that the first well defined wave of this epidemic started in different parts of the world between the months of January and June, 1918, the largest number of outbreaks taking place finally about the middle of June.

There is no complete interval of freedom between the first and second waves, a thing which we are inclined to believe probably never occurs, but the first wave declined very susceptibly.

By September and early October, the second wave which was the really destructive one in this epidemic, had gathered its full velocity. In the United States it came at that time with such sudden force that it appeared as the first onset of the epidemic, the importance from an epidemiological point of view of the earlier outbreak mentioned above not being generally appreciated at the time. The following chart taken from the article on the epidemiology of influenza by Frost which has been repeatedly quoted above, illustrates the manner in which the outbreak appeared in Boston, Washington, and San Francisco. Events identical in principle occurred in Philadelphia and New York, beginning at about the same time. The New York curve was, however, much less extensive than that which occurred in Philadelphia at this time, and the curve as charted by Frost for

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St. Louis is a little later in advent, did not reach its maximum until the middle of December and was much less high than either of the others. This wave seems to have affected the entire world, and before the end of October had swept over Russia, China, South Africa, and parts of South America.

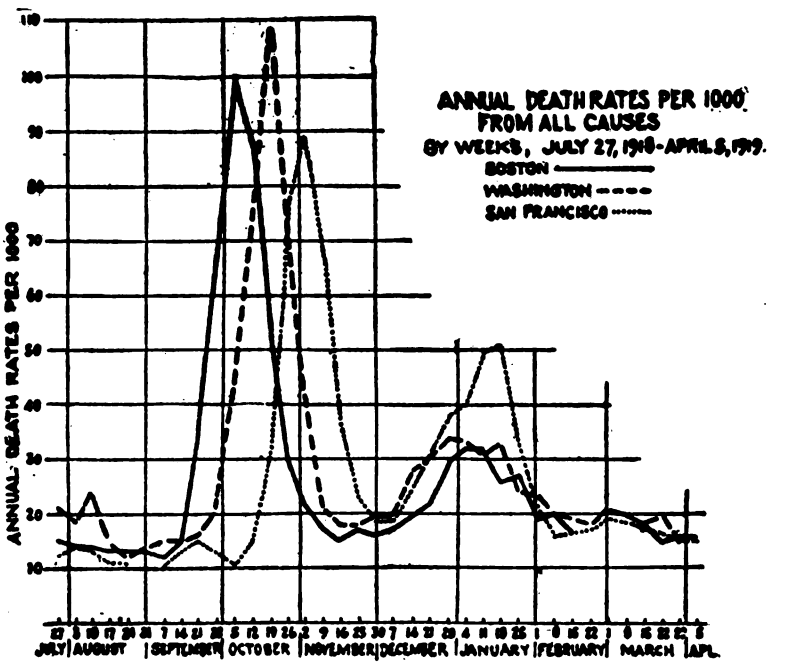

Chart taken from article by W. H. Frost, The Epidemiology of Influenza, U. S. Public Health Reports, August 15, 1919, no. 550, p. 1823–1836.

The second wave was also present in India, reaching its greatest intensity in the central, northern and western parts of the Indian Empire. The greatest number of deaths in India seem to have occurred in October and November, and by November was on the decline in all parts of India. By the end of the month, mortality had become almost normal. In Great Britain the second wave appears to have begun a little later than in America, according to McNalty beginning in October, reaching its maximum in the last week of

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October, and lasting about three or four weeks. By the end of December it had practically ceased.

A third wave followed almost immediately upon the second in many parts of the world, in Great Britain appearing so soon after the decline of the second that there was hardly any interval. It began approximately in the latter part of January, reached its height in the middle of February and had come down to almost normal by the beginning of April.

Another rise took place in America also in the month of January during which over 50,000 cases were reported from 17 states for one week, over 59,000 in the following week.

It is not our intention to attempt a statistical tabulation of the epidemic throughout the world at this time, further than to indicate that three very distinct waves occurred in rapid succession in most parts of the world in which epidemic studies were made. But this did not by any means end the history of this epidemic. In the fall of 1919 and the beginning of the year 1920, a very distinct rise of influenza cases again occurred in the United States. A general increase of cases as reported to the United States Public Health Service from the various state and city officers of public health is indicated in the tabulations of early January of this year which grew materially larger in February and declined in March. It is more than likely that recrudescences will continue to occur for some time, especially in crowded centers.

The mortality in the second wave was enormous. Pearl estimates that in the United States alone, the deaths from the influenza epidemic were not less than 550,000, "which is approximately five times the number (111,179) of American soldiers officially stated to have lost their lives from all causes in the war." A fair index of the severity of the epidemic can be gathered from the surgeon general's report. Influenza together with its complications is charged in this report with over 600,000 admissions of American and native troops for the year 1918. The total rate was 273.52. It caused 23,007 deaths. If to these are added deaths from bronchitis. bronchopneumonia, lobar pneumonia, and other conditions probably secondary to influenza, the total number of deaths would be 39,371. Approximately 82 per cent of all the deaths could be attributed to acute respiratory

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diseases. An idea of the death rate in India as taken from the report of Major Norman White (Bulletin of International office of Public Hygiene, Paris, May, 1919, p. 471–490) can be gathered from the attached table taken from this report as quoted by the United States Public Health Service.

PROVINCE	POPULATION (CENSUS OF 1911)	ESTIMATED NUMBER OF DEATHS FROM INFLUENZA	INFLUENZA DEATHS PER 1000 POPULATION
Ajmere-Merwara	501,395	33,407	66.6
Central Provinces and Berar	13,916,308	790,820	56.8
Delhi	416,656	23,175	55.6
Bombay	19,587,383	900,000	45.9
Punjab	19,337,146	816,317	42.2
Northwestern Frontier	2,041,077	82,000	40.0
United Provinces	46,820,506	1,072,671	22.9
Coorg	174,976	3,382	19.0
Madras	40,005,735	509,667	12.7
Assam	6,051,507	69,113	11.4
Bihar and Orissa	34,489,846	359,482	10.3
Burma	9,885,853	60,000	6.0
Bengal	45,329,247	213,098	4.7
Total for British India	238,527,635	4,933,132	20.7

Table taken from Report of Major Norman White, Bulletin of the International Office of Public Hygiene, Paris, May, 1919, p. 471–490.

The problem of immunity in influenza and its epidemiological significance

The explanation of the peculiar phenomenon of successively fading waves, of course, suggests the gradual development of immunity. This would be the simplest explanation and the one on the basis of which we could reason with some clearness. The question, therefore, of whether an individual and, therefore, a community as a whole develops immunity upon an attack of influenza has been the subject of many inquiries. To base any opinion upon the numerous reports of second attacks in individuals would be entirely misleading. The writer himself believes that he had three attacks during the last pandemic; the first and second mild ones, and the third complicated and, therefore, severe; and innumerable others with whom he has spoken have had similar experiences. But, although such observa-

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tions indicate with great definiteness that any immunity resulting from an attack of influenza can be a relative one only, and far less protective than the immunity conveyed by an attack of typhoid fever, smallpox, etc., a judgment of the problem as a whole can be obtained only by statistical studies of large numbers of people during the secondary waves. For even a very limited immunity might be sufficient to prevent infection in a majority of people who, in the ordinary course of association with others, are subjected to very indirect contact with minute doses of a virus which has often attenuated by conditions outside the body; and this might be sufficient to determine the difference between true epidemic prevalence and a limited, sporadic sick rate.

It is a fact that Germany and France were spared to a great extent in the spring of 1891 when North America and England suffered more severely. Parsons believes that his studies have shown definitely that there is a transitory state of resistance in a population that has been thoroughly permeated by the first wave. In his analysis in England he found that a number of communities that had suffered severely during the early epidemics were afflicted but slightly during the second, and vice versa. At Winton near Manchester at a boys' school there was a serious outbreak in March, 1890, during which 171 out of 589 children came down with the disease. In 1891, this school had almost the same inmates, 449 of the children in attendance at that time having been there throughout the earlier epidemic. In 1891, there were only 25 cases; and only 4 of the 150 who had had the disease in 1890 had it again in 1891. Two hundred and ninety-nine, who did not get the disease during the first epidemic, although thoroughly exposed, were perhaps insusceptible, since only 17 of these came down during the second wave. Conversely, a town on the Tye which escaped lightly during the first two waves, suffered heavily during the third. In Brighton there was a low death-rate during the first epidemic, and a higher one during the second and third waves; similar facts are cited for Portsmouth and Plymouth. In the St. Quentin prison epidemic which we have mentioned above, Stanley states that the second epidemic was less severe than the first, and the third far less severe than the second and, in analyzing these facts further, he finds that the men who entered prison after the first

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epidemic had subsided, were attacked in greater numbers than those that had been there before, although there were more of the latter than the former. Frost has studied immunity conditions during the last epidemic, a matter that is still fraught with great difficulties because of the incompleteness of records of the second and third waves at the present time. He made a canvass of many thousands of people in Baltimore between November 20 and December 11, 1918, and a second inquiry during January among 320,600 people; 724 cases of influenza were found to have occurred since his first survey. Of these only 26 were confirmed by reliable methods as having been true second attacks, and in not all of these was the diagnosis absolutely definite. He states that in view of the fact that "23 per cent of the population had had influenza previous to December 11, the proportion of second attacks should have been very much greater if no immunity had been acquired." Warren T. Vaughan has made an excellent and extensive analysis of the literature on this question in which he has collected a considerable number of reports which point in the same direction as the studies of Parsons and of Frost quoted above. Thus, the observations of Lemiere and Raymond, of Gibon, of Dopter, of Opie, Barthelemy, of Hamilton and Lennard, of Niven and others, all indicate that influenza leaves the individual and, therefore, the community through which it has swept, relatively more resistant than normal for a limited period. This period is appraised by Warren T. Vaughan as not shorter than three months, the acquired resistance gradually and rapidly fading thereafter. Such a conception would explain the apparently contradictory results of Jordan and Sharp, and of some observations of Frost, courteously placed at our disposal by him in a letter dated June 18, 1920. In a recent paper (Journal of Infectious Diseases, May, 1920, p. 463) Jordan and Sharp have analyzed the incidence of influenza, in subsequent waves, at the Great Lakes Training Station and at Camp Grant at Rockford, Illinois. In each of these places they divided the men into groups of those attacked and those not attacked in 1918–1919, and compared the incidence among these two groups with the respective incidence in January, 1920. Their results indicate that no marked immunity exists twelve to fifteen months after its attack. Frost states that, "in Baltimore those persons who were attacked during the 1918 to

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1919 epidemic showed no relative immunity during the epidemic of 1920." This is not therefore in contradiction to the earlier Baltimore studies cited above, since in that case the interval between the epidemic waves was not more than about three months.

It thus appears that, as far as we can gather from careful studies of many workers in different parts of the world, a definite increase of resistance if left behind after an attack of influenza which, though insufficient to protect all individuals, is still adequate to leave the community in a condition of relatively high resistance for a limited period. This period is variously estimated as approximately three or four months, and is certainly less than one or two years.

The bearing of such an immunity upon periodicity and wave-like curves of influenza epidemics is obvious.

The problem of the fluctuation of virulence of the virus

In the analysis of the conditions which govern the rise, fall and disappearance of epidemics, however, account must be taken of another influence, the reciprocal of the immunity factor, namely, the possible fluctuations in the virulence of the causative agent. It is perfectly clear to every one who has studied epidemics that the development of immunity alone cannot satisfactorily explain many of the peculiar manifestations of the outbreaks. Thus, even in epidemics in which the disease leaves behind a permanent immunity and in which, therefore, survivors represent an ever increasing non-susceptible bulwark of transfer between the infected and the susceptible populations, the decline of epidemics is not often a simple downward curve, and the mortality percentage declines with the morbidity. This last fact we have noticed particularly in typhus epidemics where, in the Serbian one for instance, a death rate of 50 or more per cent at the height of the outbreak declined to between 15 and 20 per cent as the morbidity became less. There are many other observations which would incline one to assume the manifestations and the general course of a prolonged epidemic are influenced as much by changes on the part of the infecting factor as they are by the acquisition of generally increased resistance.

The analysis of this problem is not an easy one. On the one hand, we know from laboratory experimentation that, in general, it is pos-

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sible to enhance the virulence of a race of microörganisms for a given species of animals by successive passages through such animals, avoiding intervening cultivation on artificial media; this, of course, provided that the organism in the first place renders the animals severely sick, or kills them. Thus, passing a pneumococcus or streptococcus from mouse to mouse, directly from the peritoneal exudate or heart's blood, will, with many races (though not with all races of streptococci) result in a considerable increase of infective power. Even a short sojourn on artificial media, interrupting this serial transmission, will definitely reduce infectiousness in many cases, as has been shown most clearly perhaps by the Barber method with anthrax bacilli. Passage through one species of animal may reduce or increase virulence for other species, according to the particular germ and animal species used, but this has no direct epidemiological bearing. Thus, it is not unlikely that as an epidemic spreads rapidly, a tremendous enhancement in the virulence of the germ may follow and the morbidity, as well as mortality increase rapidly. Such an enhancement of virulence by rapid transmission directly from man to man is entirely analogous to repeated animal passage, and as an excellent epidemiological example of such a case, Warren Vaughan cites the havoc played by streptococcus hemolyticus in American army camps after it had been disseminated for some time as a secondary invader of measles, subsequently acquiring virulence which enabled it to become an independent etiological agent or a fatal primary respiratory disease.

Such an enhancement of virulence, however, will rapidly reach a maximum and at the time when this maximum is reached, the general resistance of the surviving community will probably have attained a level somewhat above normal. In a disease like influenza where initial susceptibility is general and mortality of the pure, uncomplicated disease is low, this increase of resistance on the part of the community may almost keep pace with the increased virulence of the organism, and under ordinary conditions the initial wave will subside when fewer and fewer of the individuals infected with the now fully virulent virus are normally susceptible.

The conditions now established are those of the approximation of a balance between virulence of infectious agent and resistance of the

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community which balance, however, is never perfectly established and, therefore, numerous individuals of relatively low resistance or who have escaped sufficient contact during the earlier period of the epidemic, are still afflicted with the disease, and among these we may assume that an increasing proportion have attained a resistance somewhat greater than normal, if not sufficient to protect completely, and this element may contribute to the lessened mortality which accompanies the declining morbidity.

At this point another well known biological principle may be introduced, a principle which has been most clearly and thoroughly discussed by Theobald Smith. Theobald Smith speaks of highly pathogenic organisms as "incompletely adapted parasites." "The less complete the adaptation to the host, the more violent the disease produced." Thus, the acuteness of an infectious disease is an evidence of the tempestuous manner in which the host is trying to rid himself of the invader, a struggle in which the bacteria develop the defenses of capsule, etc., and the offensive weapons of poison formation and perhaps rapid multiplication. As long as this reaction on the part of the bacteria carries the upper hand the increase in virulence will continue. Conversely, however, as Theobald Smith points out, indeed, has long pointed out in some of his former papers, the chronicity of a disease is largely dependent upon an adaptation between host and invader in which the reaction to the parasite is less violent, and a condition approaching more and more closely to a sort of symbiosis, is established. As Theobald Smith puts it in a recent paper which is also quoted by Vaughan "there is a struggle on the part of the parasites to adapt themselves and to establish some equilibrium between themselves and their host;" again, "the final outcome is a harmless parasitism or some disease of little or no fatality unless other parasites complicate the invasion."

Such adaptation unquestionably takes place. On the other hand, it cannot take place unless host and invader are in contact at, at least, an approximate balance for periods longer than the ordinary acute infectious disease. During the rapid rise of an epidemic, therefore, while the organisms responsible are passing rapidly through a large series of susceptible individuals in whom death or recovery takes place, the virus transmitted rapidly from person to person,

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developing its offensive properties to a high degree, overcomes the defenses of its new hosts too rapidly to permit of much mutual adaptation. Later, as the community becomes more resistant, infections are apt to become more subacute and chronic and carriers may be established, and under such conditions the process of biological adaptation which in the course of time may result in conditions almost symbiotic, are perhaps responsible for the entirely altered manifestations of epidemics.

It is quite possible, therefore, not only in influenza but in other epidemics, that after the initial wave has reached its peak and the organisms attained full virulence, their subsequent spread consisting in a more and more delayed passage from susceptible to susceptible individual, their sojourn in contact with the tissues and secretions of cases and carriers and the slower and less violent progress of the infections in partially immunized individuals may lead to a gradual adaptation, resulting in a new balance between the invasiveness of the causative agent and the resistance of the individual.

It is quite conceivable, then, that if the immunity is a rapidly fading one, as in influenza, organisms of considerable virulence, smouldering in carriers or in mildly reacting partially immunized individuals, may pass through a new period of violent spread as the susceptible percentage is again developed to a larger extent.

In influenza, we are confronted with a particularly difficult problem in that, as we have seen above, we are in possession of no definite knowledge concerning the causative agent. As far as the influenza bacillus, itself, however, is concerned, while we are, of course, entirely in doubt as to its etiological significance, its unquestionable fluctuations in virulence are of considerable interest. Recently, in our own laboratory, J. T. Parker and Frederic Parker, Jr., studied a meningeal strain of influenza which was obtained originally from the meninges of a child which died at the Nursery and Child's hospital in New York. This organism was kept alive on artificial media for some six weeks and then used in a series of experiments on rabbits. Intratracheally injected into rabbits, this bacillus produced fatal disease, the organism appearing in the pleura and usually in the general circulation of the animals. Within 6 rabbit passages with the pleural exudate of previously killed rabbits, the organisms acquired a virulence so high

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that less than 0.05 cc. of pleural exudate would kill the rabbits in a short time, sometimes with pneumonia, sometimes passing through the lungs and causing a general septicaemia without noticeable pathological changes in the lungs. On further preservation in rabbit's blood media for about two weeks longer, this organism again lost its virulence to such an extent that lately large amounts injected into rabbits produced no noticeable effect.

It is not supposed that these considerations will throw any considerable light upon the fluctuation of epidemic waves in influenza, but they are inserted merely to indicate the lines of thought and experimentation along which these problems may eventually be elucidated.

Summary

I have sketched the epidemiology of this disease in a fragmentary way only. I have neither the material nor am I sufficiently versed in statistical studies to go more deeply into this phase of the subject. Furthermore, it is too early to attempt to complete analysis of such records, which are being carefully worked over by statisticians at the present time and will be published in due time with greater accuracy than I could bring to bear upon them.

It is quite probable that influenza will continue to be prevalent in outbreaks of varying intensity all over the world for some years to come, and that the disease will remain endemic in a scattered, sporadic manner for many years after that. May we hope that etiological and epidemiological work which is being followed so assiduously all over the world at the present time will furnish us with more competent methods for prevention and delimination before the world is visited by another pandemic.

The writer is indebted to the surgeon general of the United States army and to Col. J. F. Siler for access to his own military reports and to those of others. A number of helpful suggestions and opinions from Dr. W. H. Frost are also acknowledged with grateful appreciation.

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REFERENCES

ABRAHAMS, HALLOWS AND FRENCH: Lancet, 1919, 1.
ADRIAN: Mitt. a. d. Granzgebiete d. Med. und Chir., 1900, Bd. 7.
ALBRECHT AND V. PREYSS: Zeit. f. Heilk., 1901, lxxxiv, 470.
ALLEN: Lancet, 1910.
ANGERER: Munch. med. Woch., 1918, 1280.
ARNETH: Med. Klin., 1919, xv, 960.
AVERY: Jour. Amer. Med. Assoc., 1919, lxxii, 476, and 1918, lxxi, 2050.
ARBUTHNOT: See THOMPSON: Annals of Influenza Sydenham Society Publication, London, 1852.
ARKWRIGHT: British Med. Jour., 1919, ii, 233, Notes by Bradford, p. 236, and Wilson, p. 237.
BARTHELMEY: Rev. d'Hygiene, etc., 1920, xlii, 41.
BÄUMLER: Cited from BECK, loc. cit.
BECK, KOLLE AND WASSERMANN: Handb. d. Microorganisms, Jena, 1st edit., 1903, Bd. 3.
BERGMANN: Deut. med. Woch., 1918, xiv, 683.
BIEDERT: Berl. klin. Woch., 1907.
BIERMER: Virchows Handbuch der Speziellen Path. und Ther., Erlangen, 1865.
BINDER AND PRELL: Munch. med. Woch., 1918, 1397, 1457.
BLAKE AND CECIL: Jour. Amer. Med. Assoc., 1920, lxxiv, 170.
BLOCH: Münch. med. Woch., 1898.
BLOOMFIELD: Johns Hopkins Hospital Bulletin, 1920, xxxi, 85.
BOGGS: Amer. Jour. Med. Sciences, 1905, cxxx, 902, Johns Hopkins Hospital Bulletin, 1905.
BRADFORD, BASHFORD AND WILSON: Lancet, 1919, 1, 169.
BRADFORD, BASHFORD AND WILSON: Quarterly Jour. Med., Oxford, 1919, xii, 259.
BROWNLEE: Lancet, 1919, 2, 856.
BURCKHARDT: Correspondenz-Blatt f. Schweizer Aerzte, Basel, 1919, xlix, 583.
CADHAM: Lancet, 1919, 1, 885.
CALDERON: Jour. Amer. Med. Assoc., 1919, lxxiii.
CANON: Deut. med. Woch., 1892.
CASE: Clinics of North America, Phil., 1918, ii, 719.
CHIARI: Prager med. Woch., 1893, Nr. 52.
CHRISTIAN: Jour. Amer. Med. Assoc., 1918, lxxi, 1565.
CITRON: Berl. klin. Woch., 1918, lv, 777.
CONNER: Jour. Amer. Med. Assoc., 1919, lxxiii, 321.
CONTANI: Zeit. f. Hyg., 1901, 26.
COUTANT: Jour. Amer. Med. Assoc., 1918, lxxi, 1566.
CROOKSHANK: Lancet, 1919, 1, 313.
DAVIS: Jour. Inf. Dis., 1906, iii, 1.
DAVIS, D. J.: Jour. Amer. Med. Assoc., 1919, lxxii, 1317.
DAY: Report to the chief surgeon, American Expeditionary Forces.
DELIUS AND KOLLE: Zeit. f. Hyg., 1897, xxiv, 327.
DESJARDINS: Report to the chief surgeon, Evac. Hosp. no. 2, December, 1918, Americ Expeditionary Forces.
DEITRICH: Münch. med. Woch., 1918, lxv, 928.
DICK AND MURRAY: Jour. Inf. Dis., 1919, xxv, 6.

Digitized by Google

DOPTER: Bulletin, Paris Academy of Medicine, lxxxiii, 415.
DUBOIS: Meningite purulente a bacille de Pfeiffer, These de Paris, 1902.
DUDGEON AND ADAMS: Lancet, 1907.
DUJARRIC DE LA RIVIERE: Comp. r. Acad. des Sciences, 1918, clxvii, 406.
EDELMANN: Wien. klin. Woch., 1918, 891.
EYRE AND LOWE: Lancet, 1919, 2, 553.
EYRE AND LOWE: Lancet, October 12, 1918.
FEJES: Deut. med. Woch., 1919, 653.
FIESSINGER: Gazette med. de Paris, 1891 and 1893.
FISCHER: Klin. Monatsbl. f. Augenheilk., Jena, 1908, 46.
FLETCHER: Lancet, 1919, 1, 104.
FLEMING: Lancet, 1919, 1, 138.
FRIEDBERGER: Med. Klinik, Berlin, 1918, xiv, 922.
FRIEDRICH: Arb. aus d. Kais Gesundh., 1894, Bd. 9.
FRIEND: Lancet, 1919, 1, 105.
FINDLAY: Lancet, 1919, 1, 113.
FOSTER AND COOKSON: Lancet, 1918, 2, 585.
FROST, W. H.: Jour. Amer. Med. Assoc., 1919, lxxiii, 313.
FROST, W. H.: U. S. Pub. Health Serv. Reprint no. 550, August 15, 1919.
FRY: Lancet, 1919, 2, 51.
FRY AND LUNDIE: Lancet, February 14, 1920, 368.
GHEDINI: Gazetta degli ospedali, 1907.
GHON AND PREYSZ: Central. f. Bakt., Bd. 32, 1902.
GIANI AND PICCHI: La Sperimentale, 1903.
GIBON: John G., Lancet, 1, 583.
GOTTSCHLICH: Deut. med. Woch., 1918, xliv, 831.
HAMBURGER: Jour. Amer. Med. Assoc., 1919, lxxi.
HAMBURGER: Report to the chief surgeon, American Expeditionary Forces.
HAMILTON AND LENNARD: Jour. Amer. Med. Assoc., 1919, lxxii, 854.
HARROP: Bulletin Johns Hopkins Hospital, 1919, 30, 10.
HEYFELDER: Wien. klin. Woch., 1890, iii, 11.
HEYROWSKY: Wien. klin. Woch., 1904.
HICKS AND GRAY: Lancet, 1919, 1, 419.
HINTON AND KANE: Bimonthly Bulletin, State Bd. Health, Mass., 1919, xxviii, 6.
HOGERSTEDT: St. Petersb. med. Wochschr., 1896.
HORDER: British Med. Jour., 1905.
HOWARD: Amer. Jour. Med. Sciences, 1898.
HOWARD: Bulletin Johns Hopkins Hospital, 1919, xxx, 13.
HUBER: Zeit. f. Hyg. u. Infektkrankh., 1893, Bd. 15.
HUNTOON AND HANNUM: Jour. Immun., 1919, iv, 167.
HUXHAM: (?)
JAEHLE: Zeit. f. Heilkunde, 1901, ii, 190.
JOCHMANN: Deut. Archiv. f. klin. Med., 1905, lxxxiv, 470.
JOCHMANN: Lehrb. der Infec., Berlin, 1914, 340.
JORDAN: Jour. Inf. Dis., 1919, xxv, 28.
JORDAN: Jour. Amer. Med. Assoc., 1919, lxxi, 674.
JORDAN: U. S. Pub. Health Serv. Reprint no. 28, xxxiv, 1919.
KAREWSKI: Cent. f. inn. Med., 1899, Bd. 20.

Digitized by Google

KAREWSKI: Deut. med. Woch., 1907.
KEEGAN: Jour. Amer. Med. Assoc., 1918, lxxi, 1051.
KINNICUTT AND BINGER: U. S. Bulletin of Health, no. 6, July., 1919
KITASATO: Deut. Med. Woch., 1918, 1419.
KLEBS: Cent. f. Bakt., 1890, Bd. 7.
KLINE: Jour. Amer. Med. Assoc., 1920, lxxiv, 1312.
KLOPSTOCK: Berl. klin. Woch., 1902.
KNAPP: Arch. of Ophthalmology, 1904, xxxiii, 386.
KOLMER, TRIST AND YAGLE: Jour. Inf. Dis., 1919, xxiv, 583.
KRETZ: Wien. klin. Woch., 1897, x, 877.
KRETZ: Zur Bakteriologie der Pyelitis, Ebenda, 1898.
KRONBERGER: Deut. med. Woch., 1919, 243.
KRUSE: Deut. med. Woch., 1894, Nr. 24.
KUINA: Wien. klin. Woch., 1909.
Lancet, 1918, 2, 455.
Lancet, 1918, 2, 645.
Lancet, 1919, 1, 72.
Lancet, 1919, 1, 520.
LECOUNT: Jour. Amer. Med. Assoc., 1919, lxxii, 1519.
LEICHTENSTERN: Influenza in the nineteenth century, 2nd edition, Sticker, Holder, Leipzig, 1912.
LEICHTENTRITT: Deut. med. Woch., 1918, 1419.
LEISHMANN: Bassett-Smith, Eyre, etc., Conf. Brit. War Office, October, 1918.
LEITNER: Wien. klin. Woch., 1918, 1155.
LEMIERE AND RAYMOND: Cited from VAUGHAN, WARREN T.: Amer. Jour. Hyg., Monog. Series I, July, 1921.
LESCHKE: Berl. klin. Woch., 1919, 11.
LEVINSON: Jour. Inf. Dis., 1919, xxv, 18.
LEVINTHAL: Zeit. f. Hyg., 1918, lxxxvi, 1.
LEVINTHAL: Berl. klin. Woch., 1918, xiv, 922.
LIEBSCHER: Prag. med. Woch., 1903, xxviii, 85, 99.
LISTER AND TAYLOR: Pub. South Afric. Inst. for Med. Res., April 30, 1919, no. 12.
LOEWENTHAL: Berl. klin. Woch., 1918, 1170.
LONGCOPE: Jour. Amer. Med. Assoc., 1919, lxxiii, 189.
LORD: Boston Med. and Surg. Jour., 1902.
LORD: Jour. Med. Res., Boston, 1908, xix.
LYON: Jour. Amer. Med. Assoc., 1919, lxxii, 924.
LYON: Tenney, Szerlip, Jour. Amer. Med. Assoc., 1919, lxxii, 1726.
MACNEAL: Arch. Int. Med., 1919, xxiii, 657.
MACNEAL AND PEASE: Report to the chief surgeon, American Expeditionary Forces.
MACNALTY AND MALLOCH: Influenza, Nelson's Loose-Leaf Medicine, 1920, i, Thomas Nelson and Sons, New York.
MADISON: Amer. Jour. Med. Wc., 1910, cxxxix, 527.
MATERNA AND PENECKE: Wien. klin. Woch., 1918, 221.
MATHERS: Jour. Inf. Dis., 1917, xxi, 1–8.
MATHERS: Jour. Amer. Med. Assoc., 1917, lxviii, 678.
MATHEWS: Lancet, June 27, 1919.
MASSIN: Strassburg, Epidemic Catarrh, 1858.

Digitized by Google

MAYER: Wien. klin. Woch., 1919, 82.
McCOY: Jour. Amer. Med. Assoc., 1919, lxxiii, 401.
McINTOSH: Lancet, 1918, 2, 695.
Meeting of the Medical Institute, Chicago, February 21, 1919.
MEUNIER: La sem. med., 1898 and 1897.
MÜLLER'S: Trachoma Bacillus.
NAUWERCK: Deut. med. Woch., 1895.
NEAL: Report to the chief surgeon, American Expeditionary Forces.
NEAL AND FRIEBERG: Report to the chief surgeon, American Expeditionary Forces.
NEUFELD: Deut. med. Woch., October 24, 1918.
NEUFELD AND PAPAMARKU: Berl. klin. Woch., 1918, 9.
NEUFELD AND PAPAMARKU: Deut. med. Woch., 1918, 1181.
NICOLLE AND LEBAILLY: Ann. de l'Inst. Past., 1919, xxxiii, 385.
NIVEN: Cited from Warren T. Vaughan, loc. cit.
NOBECOURT ET PAISSEAU: Arch. gen. de. med., 1905.
OKAWARE, TANAKA, WATANEKE, KOYAMA AND SATO: Kitasato Arch. f. Exp. Med., 1918, ii, 235.
OLITSKY AND GATES: Jour. Amer. Med. Assoc., 1920, lxxiv, 1497.
OLITSKY AND GATES: Jour. Exper. Med., 1921, xxxiii, 125, no. 2.
OLITSKY AND GATES: Jour. Exper. Med., 1921, xxxiii, 361 and 373, no. 3
OLITSKY AND GATES: Jour. Exper. Med., 1921, xxxiii, 373, no. 3.
OLITSKY AND GATES: Jour. Exper. Med., 1921, xxxiii, 713, no. 6
OLITSKY AND GATES: Jour. Exper. Med., 1921, xxxiv, 1, no. 1.
OLITSKY AND GATES: Jour. Exper. Med., 1922, xxxv, 1, no. 1.
OLITSKY AND GATES: Jour. Exper. Med., 1922, xxxv, 553, no. 4.
OPIE: Jour. Amer. Med. Assoc., 72, 108 and 556, 1919.
OPIE, FREEMAN, BLAKE, SMALL AND RIVERS: Report to the surgeon general. Reported in the Jour. Amer. Med. Assoc., 1919, lxxii, 168.
ORTICONI, BARBIE AND AUGE: Presse Medicale, Paris, 1919, xxvii, 247.
ORTNER: Die Deutsche Klinik, 1903, ii, 417.
OVAZZA: Policlinico, Rome, xxvi, 271.
PARK: Jour. Amer. Med. Assoc., 1919, lxxiii, 318.
PARK AND WILLIAMS, ETC.: Amer. Jour. Public Health, 1919, ix, 45.
PARKER, J. T.: Jour. Amer. Med. Assoc., 1919, lxxii, 476.
PARSONS, H. F.: Further report on the influenza epidemics of 1889–1890, 1891 and 1891–1892, Local Government Board, London, 1893.
PEARL, RAYMOND: U. S. Pub. Health Serv. Report no. 548, August 8, 1919.
PEREZ: Deut. Zeit. f. Chir., 1902 and 1903, Bd. 63, 64, 66.
PFEIFFER: Deut. med. Woch., 1892, xviii, 28.
PFEIFFER: Zeit. f. Hyg., 1893, xiii, 357.
PFEIFFER with BECK: Deut. med. Woch., 1892.
PFUHL: Berl. klin. Woch., 1892.
PFUHL: Deut. med. Woch., 1895.
PFUHL: Zeit. f. Hyg., Bd. 26, 1897.
PFUHL with WALTER, Deut. med. Woch., 1896.
POPPELMANN: Deut. med. Woch., 1919, 379.
POSSEK: Wien. klin. Woch., 1909.
POULET: Bull. gener. de therapeutique med., 1893.

Digitized by Google

PRITCHETT AND STILLMAN: Jour. Exper. Med., 1919, xxix, 259.
RAPPOPORT: Jour. Amer. Med. Assoc., 1919, lxxii, 633.
ROBERTS AND CARY: Jour. Amer. Med. Assoc., 1919, lxxii, 922.
ROOS, C.: Jour. Immun., 1919, iv, 189.
ROOS: Report to the chief surgeon, American Expeditionary Forces.
ROSE: Lancet, 1919, 1, 421.
ROSENAU, M. J.: Jour. Amer. Med. Assoc., 1919, lxxiii, 311.
ROSENBAUCH: Klin. Monatsbl. f. Augenheilk., 1908, 46.
ROSENOW: Jour. Amer. Med. Assoc., 1919, lxxii, 1604.
ROSENTHAL: Comp. rend. de la Soc. de Biol., 1903, lv, 1500, also, 1900, lii, 266.
ROSTOWYEW: Mitteilungen, a. d. Grenzbeg., der Med. und Chir., Bd. 15, 1906.
SAATHOFF: Münch. med. Woch., 1907.
SCHELLER: Central f. Bacter., Orig., 1909, l, 503.
SCHMIDT: Wien. med. Woch., 1918, 1450.
SELTER: Deut. med. Woch., 1918, 932.
SLAWYK: Cited from LEICHTENSTERN: Influenza in the nineteenth century, Leipzig, 1912.
SLEVOGT: Jena, 1712.
SMITH, FRED: Jour. Amer. Med. Assoc., 1919, lxxiii, 1685.
SMITH, THEOBALD: Transact. Assoc. of Physicians, 1921.
SPAT: Berl. klin. Woch., 1907, 44.
STANLEY: U. S. Pub. Health Serv. Report, no. 19, xxxiv, May 9, 1919.
STALLYBRASS: Lancet, 1920, i, 372.
STANGL: Jour. Amer. Med. Assoc., 1919, lxxiii, 1048.
STICKER: Encyclopaedie der praktischen Medicin, Bd. 2, Wien, 1906.
STOLL: Jour. Amer. Med. Assoc., 1919, 478.
STURROCK: British Med. Jour., 1905.
SÜSSWEIN: Wien. klin. Woch., 1901, xiv, 1149.
SYDENHAM: The epidemic coughs of the year 1675, etc. From the works of Thomas Sydenham, 1675.
TAYLOR, KENNETH: Report to the chief surgeon, American Expeditionary Forces.
TAYLOR, RICHARD: Cited from MacNeal: Archives of Int. Med., 1919, xxiii, 657.
TEDESCO: Cent. f. Bakt., I, Orig., 1907, 43.
TEISSER: L'influenza en 1889–1890 en Russie, Rapport de mission, Paris, 1891.
THOMPSON: Annals of Influenza, London, 1852.
TRAWINSKI AND CORI: Wien. klin. Woch., 1918, 1251.
UHLENHUTH: Med. Klinik, Berlin, 1918, xiv, 777.
VALENTINE AND COOPER: Reprint Series no. 84, N. Y. Pub. Health Res. Lab., December,
VALENTINE AND COOPER: Reprint Series no. 84, N. Y. Pun. Health Res. Lab., December, 1919.
VAUGHAN AND PALMER: Military Surgeon, 1918, xliii, no. 4.
VAUGHAN AND PALMER: Jour. Lab. and Clin. Med., 1919, iv, 647.
VAUGHAN, WARREN T.: Influenza and epidemic study. Amer. Jour. Hyg., Monographic Series I, July, 1921.
WASSERMANN: Deut. med. Woch., 1893, xix, 1201.
WASSERMANN: Deut. med. Woch., 1900.
WEICHSELBAUM: Wien. med. Woch., 1890.
WEICHSELBAUM: Wiener med. Blatter, 1890.
WEICHSELBAUM: Handb. per path. Micro., Bd. 3, Jena, 1903.

Digitized by Google

WEISS: Report to the chief surgeon, American Expeditionary Forces.
WHAL, WHITE AND LYALL: Jour. Inf. Dis., 1919, xxv, 419.
WHITE, MAJOR NORMAN: Bulletin International Office of Pub. Hyg., Paris, May, 1919, 471–490.
WIESNER: Mitt. a. d. Deut. Oetser. Staatsamt. f. Volksgesundheit., 1918. 10.
WIESNER: Wien. med. Woch., 1918, 1969.
WINCHELL AND STILLMAN: Jour. Exp. Med., 1919, xxx, 497.
WIRGMAN: Lancet, 1919, 1, 357, and Lancet, 1918, 2, 324.
WOHLWILL: Münch. med. Woch., 1908.
WOLBACH: Bull. Johns Hopkins Hospital, 1919, xxx, 104.
WOLLSTEIN, M.: Jour. Exper. Med., 1905, vii, 335.
WOLLSTEIN, M.: Jour. Exper. Med., 1906, viii, 681.
WOLLSTEIN, M.: Jour. Exper. Med., 1915, xxii, 445.
WOLLSTEIN, M.: Jour. Exper. Med., 1919, xxx, 555.
WOLLSTEIN AND GOLDBLOOM: Amer. Jour. Dis. Child., 1919, xvii, 165.
WUTZDORFF: Arb. a. d. Kais.-Gesund., 1894, ix, 414.
WYNEKOOP: Jour. Amer. Med. Assoc., 1903, xl, 574.
WYNEKOOP: Chicago Medical Record, 1903, xxiii, 343.
YAMANOUCHI, SKAKAMI AND IWASHIMA: Lancet, 1919, 1, 971.
ZINSSER, HANS: Report to the chief surgeon, American Expeditionary Forces.
ZUR NEDDEN: Klin. Monatsbl. f. Augenheilk., 1903, xli, 209.

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THE SPECIFIC DYNAMIC ACTION OF VARIOUS FOOD FACTORS

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I. INTRODUCTION

The appetite controls the ingestion of food so that an average man may pass through decades without material gain or loss of weight. The sense of appetite must be an extremely delicate regulator to prevent the gain or loss of body fat through the intake of too much or too little energy in the food.

Life depends upon the continued existence of the component cells of an organism, and these cells must be nourished with food if they are to survive. Phenomena of life are phenomena of motion. The motions within the living cells are maintained at the expense of energy derived from the oxidation of fragments of broken down food-stuffs, that is to say, of disintegrated particles of protein, fat and carbohydrate.

The inquiry, therefore, ultimately concerns the utilization of materials present in the fluid bathing the individual cells.

A broad, clear visioned conception of the underlying fundamentals has been presented by Rubner (33) in his volume on the "Nutritional

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Physiology of the Yeast Cell." He presents comparative figures establishing the Law of Surface Area and these may advantageously be studied.

	Calories produced per square meter of body surface in 24 hours at 15°C.
Man	1042
Pig	1078
Dog	1039
Rabbit	917
Guinea-pig	1246
New-born mouse	1122

These comparative values of the heat production per square meter of surface are based upon the general assumption that the surface is a factor of the mass following the formula

$$\text{Surface} = \sqrt[3]{\text{Volume}^2}$$

Those investigators, present or future, who would upset the validity of the law that in the resting mammal the heat production is proportional to the surface area, should demonstrate the falsity of the general relations exhibited above if they wish to establish their case.

Rubner has carried the investigation of the metabolism from the gross results obtained in highly developed mammals to the metabolism which may be computed as arising daily from a square meter of cell surface. These results may be thus summarized:

	WEIGHT	CALORIES PER KILOGRAM	CALORIES PER SQUARE METER CELL SURFACE	CELL SURFACE IN SQUARE METERS PER KILOGRAM
Horse	450.0 kgm.	11.1	0.03	
Man	70.0 kgm.	30.0	0.2	150
New-born mouse	1.0 gram	654.0	3.69	
Yeast cell (38°)	0.000,000,000,5 gram	1743.0	3.0*	600

* Rubner gives this figure as 1.25, which is apparently an error in calculation.

The heat production of a unit of mass of yeast is therefore threefold that of a new-born mouse, 58 times that of a man and 157 times that of a horse.

The heat production per square meter of cell surface, however, is quite the same in the yeast cell and in the new-born mouse, but it is

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15 times greater in the yeast cell than in man and is a hundred times greater than in the horse.

Rubner has further calculated the quantity of protein and sugar absorbed by a square meter of cell area and also the quantity of cane-sugar necessary to furnish cells presenting a square meter of surface with sufficient energy for the maintenance of life for 14 hours.

These values may be thus tabulated:

	CALORIES PER SQUARE METER CELL SURFACE	CANE-SUGAR EQUIVALENT GRAMS	PROTEIN FOR MAXIMAL GROWTH PER SQUARE METER CELL SURFACE
Horse	0.03	0.007	0.002
Man	0.2	0.05	
New-born mouse	3.69	0.89	0.030
Yeast cell	3.00	8.38*	0.948

* Anaerobic.

The yeast cell achieves its maximum activity in solutions of cane-sugar which vary between 2.5 to 20 per cent in concentration. Within these limits the fermentation process is independent of the concentration of the solution. When the yeast cells are suspended in a solution of cane-sugar having a strength of 20 per cent., the quantity of sugar contained in a film 0.04 mm. thick would afford a sufficiency of nourishment for their support during twenty-four hours. In like manner it may be calculated that in man, whose cells are bathed in a liquid containing 0.1 per cent of sugar, the quantity necessary to support life for the period of one day would be contained in a layer which, if spread around a cell, would have a thickness of 0.05 mm.

If one continues this manner of calculation it may be estimated that the quantity of sugar in a 0.1 per cent solution necessary fully to maintain an average active cell in the human body during a period of one minute would be present in a film 1/300,000 mm. thick or one having approximately 1/200 of the diameter of a red blood corpuscle. It is probable that the entire circuit of the blood is accomplished in between twenty and thirty seconds. The blood plasma in man is separated from the tissues by a capillary wall so thin that no computation of its size has been made. The existing experimental evidence

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indicates that there is no oxidative disintegration with resultant heat production in the blood itself. The blood stream is the transportation system to the ultimate consumers, which are the individual tissue cells.

One can therefore picture a tissue cell whose requirement for maintenance for a minute may be held in a film of fluid containing 0.1 per cent sugar solution having the thickness of 1/200 the diameter of a blood cell, and that this fluid may be replenished through an indeterminably thin capillary wall by the diffusion of materials such as sugars, fats and amino-acids passing in a constant stream, no part of the current of which rests in a given capillary for a time exceeding two seconds. One can well imagine that if the nutrient fluid should contain food particles in abundance, the nutritive condition in the cells might be modified thereby. In what way do these body cells react to an increased bombardment by glucose, by fat, by glycocoll, by alanin, by acetic acid or by lactic acid? And how are the results obtained to be interpreted?

In 1913 Rubner (34) spoke as follows in the Prussian Academy of Sciences:

> To follow nutrient particles to the cells, to measure them quantitatively and to vary them experimentally, belongs to the unsolved problems of today. It is scarcely to be expected that the difficulties standing in the way will soon be overcome.

Though the methods employed be crude and the results obtained be often merely suggestive, yet it is these problems with which the present paper deals.

Under conditions of fasting or under "post-absorptive" conditions when there is no longer any food in the intestine, when the sugar content of the blood is regulated by the liver, when amino-acids are produced in but small quantity, when fat is available in probably restricted amount, if, under these conditions, the heat production of the quiet, resting organism be determined, it will be found that a constant level of minimal metabolism has been established. This level is known as the *basal metabolism*. Ingestion of the three classes of the food-stuffs, whether these be fats, carbohydrates or proteins, increases the quantities of fats, of sugar or of amino-acids in the

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blood and therefore in the nourishing plasma surrounding the tissue cells and, under these influences, the production of heat by an animal increases, as may be measured by weighing the oxygen absorbed or by determining directly the heat produced. The increase of heat production under these influences is different with the different kinds of food-stuffs administered. Rubner has defined the increase in the heat production of the organism under the influence of a food-stuff as being the *specific dynamic action* of that food-stuff. It is necessary to picture the plethora of the particles of a food-stuff reaching the living cells and to consider the reaction of the cells to this changed nutritive environment. In other words, the heat production increases when there is a heightened concentration of glucose or of fat or of certain amino-acids in the nutrient fluid bathing the cells of the organism. What is the cause?

A. Rubner's conception of the specific dynamic action of food-stuffs

One of the earliest papers by Rubner (35) is entitled "The Substitution Values of the Principal Organic Food-stuffs in the Animal Body." In this paper the constancy of the fasting metabolism is noted and Rubner comes to the conclusion that when fat, carbohydrate or protein is ingested, each replaces in the body metabolism isodynamic equivalents of body fat or body protein which would otherwise have been consumed in fasting. In other words, 100 calories contained in ingested fat would prevent the destruction of 100 calories contained in body fat, or 100 calories contained in sugar would have effected the same result. This was the basis of Rubner's *isodynamic law*. Throughout Rubner's writings one finds this conception of a fundamental *basal metabolism* attuned to the minimal requirements of cell life, upon which other forms of metabolic activity are superimposed.

When at a later date he (36) formulated the doctrine of the specific dynamic action of the individual food-stuffs, Rubner held to the conception that the basal metabolism was not itself augmented by the ingestion of food, but that it was supplemented by the addition of heat resulting from the cleavages and oxidations of minor fragments produced in the destruction of food particles. According to Rubner

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when 100 calories are administered to a dog in the form of sucrose (cane-sugar), the heat production is increased by 5.8 calories. He illustrated the formation of this small quantity of extra heat by comparing it with the quantity of heat eliminated when glucose and fructose are formed as cleavage products of sucrose. He believed that similar cleavages of ingested fat produced the extra 12.7 calories which he observed were liberated in the body when 100 calories in fat were ingested. His conception was that the basal metabolism was satisfied by the utilization of sugar or fat radicles, and that any heat produced aside from that was extra heat which did not involve cellular dynamics. His subsequent discovery that during the life of the yeast cell the major part of the energy is liberated within the yeast cell itself and a small part only is due to enzymotic fermentation outside of the cell, contributed to his mental picture of the strictly dual character of (1) the satisfaction of the fundamental energy requirement and (2) the production of extra heat (36a).

When protein was administered to a dog Rubner interpreted the very great increase in the heat production as being due to the fact that only a part of the protein metabolized could be used to furnish the basal metabolism with life giving energy, whereas a goodly portion of the fragments of the amino-acids were oxidized so that they yielded free heat which could not be utilized for cellular dynamics. For example, in so far as sugar was produced from protein it could be used in the service of the maintenance of the basal metabolism.

Rubner (36) furthermore discovered that the great rise in protein metabolism which Lusk had shown to be a feature of the metabolism in phlorhizin glycosuria in a fasting dog was accompanied by a greatly increased heat production although no protein had been ingested. Rubner calculated the increased heat production for every 100 calories of protein ingested or metabolized, as follows:

	Increase in calories
Meat protein	30.9
Gelatin	28.0
Body protein (phlorhizin glycosuria)	31.9

A very important relation brought out by Rubner is that when the environmental temperature is lowered in the fasting dog the heat production is thereby increased, but such an increase does not take

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place if the dog has been given meat in quantity. The following experiment illustrates this point:

ENVIRONMENTAL TEMPERATURE	FOOD	CALORIES PER KILOGRAM
7°	None	86.4
30°	None	56.2
7°	81 calories in meat per kilogram of dog	87.9
30°	81 calories in meat per kilgoram of dog	83.0

The basal metabolism in this instance was 56.2 calories. On reducing the environmental temperature from 30° to 7° it was increased through the reflex influence of cold (the *chemical regulation of temperature*) to 86.4 calories. On giving meat the heat production rose from 56.2 to 83.0 calories if the environmental temperature were 30°. But if the meat were given at an environmental temperature of 7° the heat production was 87.9 calories or practically the same as 86.4 calories found when the dog was fasting in the cold. This experiment reinforced Rubner's doctrine of a fundamental basal metabolism which must be provided with definite fuels. The condition of extra heat requirement, such as is produced through the influence of cold, could be supplied not only from the body stores of fat in fasting, but also from those extra heat producing metabolites of protein which are not directly concerned in the support of cell life.

The theory of Rubner appeared fascinating and was wholly accepted by me in the first two editions of the "Science of Nutrition."

An important contribution of Rubner to the subject of the increased heat production after giving food was the demonstration that the factor of intestinal activity, "Darmarbeit" in the sense of Zuntz (27), had nothing whatever to do with the rise in heat production Thus Rubner (36) demonstrated that administration of bones or of Liebig's extract of beef or of the quantity of water contained in the meat previously given to the dog were without influence upon the production of heat.

Lusk (20) has shown that when urea is given there is no increase in the heat production and that sodium chloride is also without influence.

The absence of "Darmarbeit" as a factor in the specific dynamic action of food-stuffs has been confirmed by others. The work of

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Benedict (6) showed that cathartics administered to men caused no increase in the basal metabolism. Johansson (17) showed that administration of glucose to a fasting man or to a diabetic individual might cause no increase in the elimination of carbonic acid, because the greater quantity of the glucose in the first instance deposited as glycogen, and in the second instance was eliminated unoxidized in the urine. Lusk (21) has also shown that the administration of glucose (up to 70 grams) or of fructose to a dog rendered diabetic by phlorizin does not increase the heat production of the animal. The extra heat production after giving sugar is therefore due neither to the absorption of the material nor can it be due to extraordinary kidney activity. Since the cells of the body are readily permeable to glucose and since glucose must diffuse into them after its administration in phlorizin glycosuria, it is evident that the phenomenon of osmosis does not contribute an increase in the heat production. This is reinforced by the fact already stated that the administration of a solution of common salt is without effect upon metabolism.

The conclusion is therefore warranted that an increased metabolism is due to the interrelation between the food-stuffs brought by the blood stream and the metabolizing cells themselves.

B. A critique of Rubner's experiments

The third edition of Zuntz and Loewy's "Lehrbuch der Physiologie" (1920) contains an article written by Zuntz on "Stoff und Kraftwechsel" which must have been revised just before he died. In this he writes:

> It follows from the comprehensive experiments of Mangus-Levy (25) that the rise in metabolism after the ingestion of fat is about 2.5 per cent of the calorie content of the same; about 9 per cent after giving starch; about 17 per cent after giving protein.
>
> Rubner found similar values.

However, Rubner's values were quite different.

	per cent
After cane-sugar	5.6
After fat	12.9
After protein	30.0

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Rubner's work was based upon metabolism experiments which continued for twenty-four hours and therefore the finer transitions which can be measured from hour to hour were not observed. No record was kept of the bodily movements of the dog within the box, and in the course of twenty-four hours this might, under certain circumstances, have become an important factor. Furthermore, in Rubner's experiments 30, 31 and 32 in which he fed to the dog a given quantity of meat, the metabolism rose 21.8 calories per kilogram of body weight and in experiments 37 and 38 the same quantity of meat ingested caused it to rise only 16.3 calories. These two figures were averaged in the computation of Rubner's results. Another element open to criticism has been set forth on another occasion. Rubner (36) himself showed that when protein is added to the body it exerts no specific dynamic action and this has been beautifully confirmed in my laboratory by Hoobler (16) after he administered "Eiweissmilch" to a baby. Rubner based his calculations of the percentage quantity of extra heat production upon the calories contained in the meat ingested, although it would appear that the controlling factor is in reality dependent wholly upon the quantity of extra protein metabolism over and above that which occurs in fasting.

If I take the values found in my laboratory and calculate them according to Rubner I find the following figures:

100 calories ingested as protein of meat increase heat production 30.0 calories (43)
100 calories ingested as fat increase heat production 4.1 calories (28)
100 calories ingested as glucose increase heat production 4.9 calories (20)

If, however, the intensity of the specific dynamic action be measured by subtracting the calories of protein of the basal metabolism from those of the hours after giving meat, and determining what relation these *extra* calories of protein metabolism bear to the total increase in calories for the hour, one finds the following relations (43):

Food	*Every extra 100 calories of protein metabolised increases the heat production in calories*
1200 grams meat	45
700 grams meat	48

This calculation merely assumes that the portion of ingested protein which is not metabolized but which replaces the "wear and tear"

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quota of the basal protein metabolism contributes no part to the "specific dynamic action" of protein. One must conclude, therefore, that about one-half of the calories of the extra metabolized protein contributes to increasing the heat production of the body. Since Lusk has shown that 51 per cent of the calories of meat protein may pass through a glucose stage, this calculation would of itself be a most perfect demonstration of Rubner's contention that the glucose obtained from protein may be used for the support of the basal metabolism, whereas the other fragments burn, liberating pure heat. Rubner's observation that the elevation of the level of metabolism was proportional to the quantity of meat given, is confirmed. The regularity of the appearance of a definite proportion of extra heat certainly gives intellectual foundation to the theory of Rubner that a part of the calories latent in protein always follows a given course.

As regards the interpretation given by Rubner of the extra calories formed by cleavage after the ingestion of fat, the suggestion is less clear, for in fasting the body lives principally upon its own body fat though at a lower level of metabolism than prevails after fat ingestion. Ingested glucose also causes a specific dynamic action, though glucose is always present in the blood and available for the production of cellular energy.

Recent experiments in my laboratory conducted with modern methods have traced the metabolism process in hourly periods and have confirmed and extended many of the early and often neglected experiments of Magnus-Levy published in 1894. It has been our experience that the experimental work of both Rubner and Magnus-Levy is accurate, but in the light of newer facts other interpretations follow.

In the account hereafter given the experimental evidence is based largely upon the author's own experience. The historical background has been presented above and more fully in the "Elements of the Science of Nutrition."

II. THE INFLUENCE OF CARBOHYDRATE ON THE HEAT PRODUCTION

It is nearly forty years since Carl Voit (41) with prophetic insight wrote as follows:

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The mass and capacity (Leistungsfähigkeit) of the metabolizing cells, on the one hand, and the quality and quantity of the food materials brought to them, on the other, determines the height of metabolism; however, the cells can only be active within certain given limits beyond which an additional food supply can no longer be destroyed.

The principal changes in metabolism are induced by the differences in the quality and quantity of the materials used by the cells as brought to them in the circulating blood. The quantity of protein brought in the blood stream is the especially influential factor, but the non-nitrogenous substances are also concerned.

These words of Voit were penned before it was conceived that the protein molecule is a mass of amino-acids bound together. Furthermore, he wrote

The requirement for energy cannot possibly be the cause of metabolism any more than the requirement for gold will put it into one's pocket. However, the production of energy has a very definite upper limit which is afforded by the ability of the cells to metabolize (42).

When glucose is given to a dog it is rapidly absorbed. Fisher and Wishart (13) found that after the administration of 50 grams of the substance in 150 cc. of water the material was nearly all absorbed within the first three hours and completely so during the fourth hour. During this last hour two things happen—a large volume of urine (100 cc.) is eliminated and glycogen in increased quantity is deposited in the liver. During the second, third and fourth hours the metabolism rises about 20 per cent but falls to the basal level during the fifth hour. It is found that the level of blood sugar rises during the first hour but, though it returns to normal thereafter, there is a dilution of the blood, as indicated by a reduced percentage of hemoglobin. The greater volume of more dilute blood therefore carries a greater largesse of blood sugar to the cells than before. The respiratory quotient during the third, fourth and fifth hours is unity, indicating that the source of energy for the living cells is glucose. With the cessation of absorption the liver assumes control of the distribution of sugar molecules in the blood stream, the respiratory quotient falls, indicating a resumption of the oxidation of fat as well as sugar by the cells and the metabolism returns to the basal level.

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These factors have led me to define this form of metabolism as the *metabolism of plethora*. Voit stated that an increase in metabolism was dependent on the flow of metabolizable material to the cells. And he also stated that the intensity of the metabolism has a well defined upper limit beyond which it was uninfluenced by additional excess of nourishing materials. This has been substantiated in the following experiments (20).

	GLUCOSE INGESTED	RISE IN METABOLISM IN SECOND HOUR	R. Q.
	grams	*per cent*	
Dog XVIII	8	0	0.91
Dog II	20	15	1.08
	50	20	0.98
	75	20	1.05
Dog I	103	20	1.02

When 8 grams of glucose were given the material caused only a slight increase in the respiratory quotient and there was evidently no such overwhelming of the body cells with an excess of sugar molecules as to cause their utilization to the exclusion of fat. In the other cases, however, the sugar was given in sufficient quantity to cause respiratory quotients near to unity or over, which demonstrates the exclusive combustion of carbohydrate instead of fat. When 50, 75 or 100 grams of glucose were given the same height of metabolism was always attained. This confirms Voit and also is in line with Rubner's discovery (see p. 313) that within wide limits the intensity of the metabolism of yeast cells is independent of the concentration of the sugar solution in which they are living.

It should be remembered that all sugars diffuse with great rapidity throughout the body. Thus, if lactose, which can not be oxidized in the body, be introduced intravenously into a dog, it is found that within half an hour 75 per cent of the injected material has diffused into the tissues (40). But it is not this movement of sugar molecules but their oxidation which is the cause of the specific dynamic action of carbohydrate, for it has been shown (21) that when 70 grams of glucose are given to a dog rendered diabetic with phlorhizin, the

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respiratory quotient may remain at 0.72 instead of rising to 1.00, the urinary sugar may rise from 1.5 to 7.9 grams per hour, and yet with all this movement of sugar molecules within the diabetic organism the heat production of the dog remains unchanged.

Johansson (17) has shown that when glucose is given to a man after prolonged fasting the carbonic acid elimination is not increased through a deposition of glycogen in the body. This experiment demonstrates that when glycogen is deposited in the organism there is no appreciable increase in the heat production.

In another series of experiments the differentiation in the behavior of various carbohydrates has been investigated. The results obtained are set forth in the following table:

The relative influence of 50 grams of glucose, fructose, sucrose, galactose and lactose upon metabolism

SUGAR	AVERAGE R. Q.	HOURS 2, 3 AND 4 INCREASE OVER BASAL PER CENT
Glucose, 50 grams	1.00	30
Glucose, 70 grams	1.04	35
Fructose, 50 grams	1.02	37
Sucrose, 50 grams	1.02	34
Galactose 50 grams	0.93	22
Lactose 50 grams	0.90	3

In this dog it is apparent that milk sugar was not utilized, probably because of the absence of lactase from the dog's intestine. It was also noted that galactose caused a lesser rise in metabolism than did either glucose or fructose, and the respiratory quotient shows this sugar to be less readily oxidized than are glucose and fructose. Of the latter two, fructose has a slightly greater power to increase metabolism than is possessed by the same amount of glucose. This attribute of fructose may lie in the fact that it must be transformed into smaller molecules before it can be converted into glucose and laid down as glycogen, whereas ingested glucose may be directly removed from the body fluids and be converted into glycogen. The formula for the conversion of fructose into glucose may thus be written:

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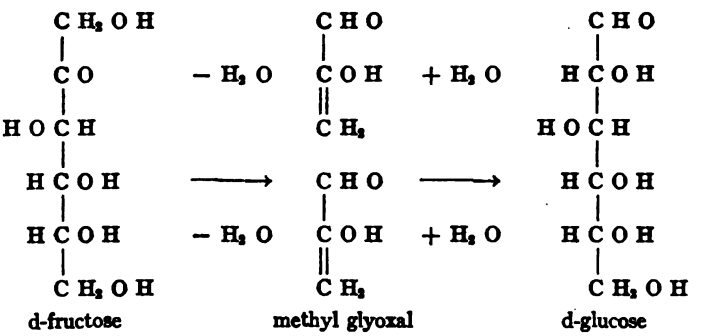
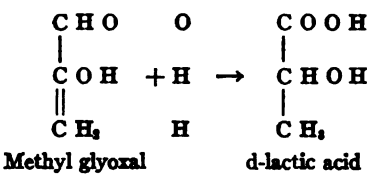


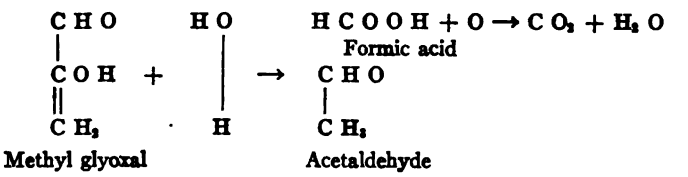
That methyl glyoxal is an important intermediary product of carbohydrate metabolism has been especially emphasized by Dakin (10) who finds that tissue rapidly converts it into lactic acid in vitro, and that it is converted into glucose and eliminated in the urine when given to a phlorhizinized dog.

If one looks further into the subject of the intermediary metabolism of carbohydrate it appears that, although methyl glyoxal may be readily converted into lactic acid according to the following formula,



yet, Levene (19) has shown that neither tissue nor leucocytes will oxidize lactic acid further.

It was originally suggested to Magnus-Levy (26) by Spiro that acetaldehyde might be an intermediary product of lactic acid metabolism. If methyl glyoxal underwent this transformation the formula would read as follows:



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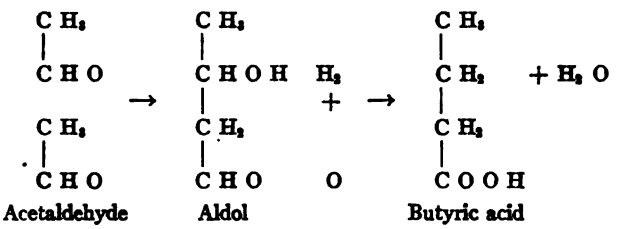
Spiro propounded this pathway of sugar destruction as a possible explanation of the synthetic construction of fat from carbohydrate, which, written in its simplest form, would present the following chemical changes:



Stepp (40a) finds that after the ingestion of a large quantity of carbohydrate the results obtained on analysis of blood serum for sugar by the optical and the reduction method do not agree and offers this as evidence that acetaldehyde radicles are present in the blood under these circumstances.

It is interesting to note at this point that, whereas acetaldehyde is convertible into glucose in the phlorhizinized dog,[1] as shown by Ringer (31), yet if it be oxidized to acetic acid (32) or reduced to ethyl alcohol (15) or by hydrolysis be converted into butyric acid (30), it is then no longer convertible into glucose.

Ringer (31) believes that acetaldehyde is the main antiketogenic substance derived from carbohydrate metabolism, and that it reacts with β-hydroxybutyric acid to form a substance containing six carbon atoms three of which are convertible into glucose.

It has been shown that when alcohol (21) or acetic acid (unpublished, see p. 335) are given with glucose to a dog the heat production rises above the level manifested when glucose alone is given by the addition of that increment of heat which either ethyl alcohol or acetic acid, when given alone, would have induced. Therefore, it seems that these two substances must be affinities of their own in the heat augmentation process which are not affected by the cleavage products of glucose. If one conceives a cleavage of carbohydrate with the production of acetaldehyde molecule, one must consider it probable

[1] My colleague, Stanley R. Benedict, has found the conversion of acetaldehyde, to be complete in the phlorhizinized dog (Unpublished; quoted by permission).

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that there is a limit beyond which its oxidation through acetic acid is not effected.

Still other unpublished experiments show that, although lactic acid ingested alone may increase the heat production, yet when given with glucose there is no augmentation above that which glucose alone produces. This is because its metabolites are of the same order as those of glucose.

The picture that presents itself, therefore, is that a glucose molecule carried by the blood stream rapidly diffuses into the cells, that it may be broken in two within the cells into methyl glyoxal molecules, thereby increasing the number of metabolizable compounds and also their chemical lability. The next step might be the conversion of methyl glyoxal into formic acid, which might at once be oxidized, and into acetaldehyde, which when present in excess of the requirement of energy for the cell might react with formic acid and be condensed into fat. Its oxidative pathway through transformation into acetic acid would then be inhibited.

Remembering these possibilities, one can consider the bearing of certain experimental results upon the interpretation of the cause of the specific dynamic action of carbohydrates. For one may explain the slightly greater increase in the metabolism of the dog after giving fructose than after giving glucose by imagining that the whole mass of the ingested fructose becomes available for the maintenance of cell activity because it must, perforce, pass through the methylglyoxal stage, whereas glucose itself could have been laid down directly as liver glycogen and thereby could have reached the blood stream and the tissue cells in lesser concentration than fructose would have done.

If carbohydrate be given in considerable quantity at a time when the glycogen reservoirs are filled and the body cells have reached their *optimum* of carbohydrate destruction, then carbohydrate is converted into fat. Such fat production may be illustrated by the following formulae:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} + O_2 = \underset{\text{Butyric acid}}{CH_3(CH_2)_2\,COOH} + 2CO_2 + 2H_2O$$

$$\underset{\text{Glucose}}{4C_6H_{12}O_6} + O_2 = \underset{\text{Palmitic acid}}{CH_3(CH_2)_{14}\,COOH} + 8CO_2 + 8H_2O$$

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The respiratory quotient when palmitic acid is formed from glucose would be 8.0. Bleibtreu (7) took into consideration the production of the glycerin and fatty acid content of animal fat and wrote the formula:

$$\begin{array}{l} 270.6 \text{ grams glucose} = 100 \text{ grams fat} + 115.45 \text{ grams } CO_2 + 54.6 \text{ grams } H_2O \\ 997.2 \text{ calories} \quad = 950 \text{ calories} \end{array}$$

I have added the caloric values and have estimated that 4.7 per cent of the original heat content of the glucose was lost in its chemical transformation into fat. From this it may be estimated that for every liter of carbon dioxide eliminated 0.80 calories are produced. Similar calculations were made by Magnus-Levy (25) in 1894, who used a formula written by Hanriot (14). He concluded that there was very little extra heat production when either carbohydrate or protein was converted into fat. That this was a true conclusion was proved by Lusk (21) from experiments in which he gave 70 grams of glucose to a dog. In one of the experiments (no. 91) the results may thus be calculated:

	HOURS AFTER GLUCOSE			
	2	3	4	All 3
Indirect calorimetry	24.52	24.91	24.81	74.41
Indirect calorimetry (corrected)	24.78	25.38	25.49	75.65
Direct calorimetry	25.31	25.63	25.12	76.06
Respiratory quotient (non-protein)	1.08	1.14	1.16	

It is evident that the correction of the heat production on account of the transformation of carbohydrate into fat introduces only a slight element of increase in the sum total of heat produced. That the calculation is sound is confirmed by the agreement between the calculations thus made and the heat as determined by direct calorimetry.

In the above experiment 1.73 liters of extra CO_2 were expired by the dog as the result of converting 8.1 grams of glucose into 3 grams of fat. In another experiment (no. 90) the production of fat from sugar was only half the above quantity, though the metabolism was practically at the same level, 75.30 calories in three hours.

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It is therefore evident that if the level of optimum metabolism is reached, the process of conversion of carbohydrate into fat involves the cells of the organism in virtually no additional heat production.

It has been suggested that acid radicles are the cause of the increase in heat production; that they stimulate the cells after carbohydrate ingestion. However, it was first shown in my laboratory by A. L. Meyer that the CO_2 combining power of the blood plasma was unchanged after giving glucose in large quantity, and repeated experiments have recently confirmed this observation. Moreover, it has also been discovered that after giving hydrochloric acid sufficient to reduce the CO_2 combining power of the blood plasma from 54 to 48 volumes per cent of CO_2 in the blood plasma, the metabolism is only very slightly increased and not at all to such an extent as is effected by glucose ingestion. It has also been suggested that when fructose is given to a diabetic the heat production is increased through the stimulating effect of acid intermediate products (5). However, Lusk (21) found no increase in the heat production of a phlorhizinized dog after giving 10 grams of fructose which was largely converted into glucose and eliminated in the urine. The intermediary metabolite, probably methylglyoxal, exerts, therefore, no stimulating effect upon the heat production. This result has been confirmed by Falta (12) in experiments on man.

Another experiment (2) of especial significance is, that when 70 grams of glucose are given to a dog and the dog forced to run at a rate of 4800 meters per hour (3 miles), the heat production of the animal is slightly less than when the animal runs in the morning without food (see p. 336). Even on the thirteenth day of fasting the cost of energy in the dog for the movement of 1 kgm. of his body weight one meter is the same as when the animal is well nourished. This may be expressed thus:

	WORK IN KILOGRAMS TO MOVE 1 KGM. 1 M.	R. Q.
Running morning without food	0.578	0.79
Running after 70 grams glucose	0.555	0.92
Running 13th day of fasting	0.584	0.73

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The respiratory quotient did not reach unity when the dog ran after glucose ingestion. It is probable that glucose reaching the cells was immediately utilized for the work of the movement and that there was no surplus of metabolizable particles to raise the metabolism of the cells. Certainly, no intermediate metabolites of glucose exercised a specific dynamic effect to lift the cellular metabolism to a higher level upon which the metabolism necessary for muscular effort had to be superimposed.

A. Summary

1. When 50 grams of glucose are given to a dog it is rapidly absorbed and glucose molecules are furnished to the body cells in increased number.

2. All sugars diffuse into the body cells with great rapidity.

3. Increased movement of unoxidized glucose molecules in diabetes is without influence upon the heat production.

4. The deposition of glycogen does not increase the heat poduction.

5. If 50, 75 or 100 grams of glucose be given to a dog it is possible to increase the heat production by 20 per cent above the basal metabolism during the hours of glucose absorption, but increasing the quantity of glucose ingested does not increase the level of metabolism, which may therefore be described as the optimum level of glucose metabolism.

6. Another dog, whose metabolism had been raised 30 per cent above the basal level after giving 50 grams of glucose, suffered an increase of 35 per cent after receiving 70 grams of glucose and one of 37 per cent after taking 50 grams of fructose. It is suggested that, whereas part of the 50 grams of glucose could have been laid down as glycogen and removed from the circulation, all of the fructose must first break up into methyl glyoxal radicles, thereby increasing the mass of these readily oxidizable metabolites.

7. If carbohydrate be given in excess it may be converted into fat, but this process transpires with only a slight energy loss and does not appreciably increase the total cellular heat production which the already reached its maximum.

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8. When lactic acid is given with glucose the total metabolism is not appreciably affected, for lactic acid is directly derivable from glucose and may satisfy the cellular affinities for this material.

9. When acetic acid or ethyl alcohol is given with glucose there is a summation of effect, the metabolism being raised by the sum of the increases which each substance given alone would induce. Possibly acetic acid and alcohol are not metabolites of glucose. If acetaldehyde be a normal product of glucose metabolism, one must conclude that there is a limit beyond which its oxidation through acetic acid is not effected.

10. Ingestion of glucose in large quantity does not reduce the CO_2 combining power of the blood and hence one can infer that acid metabolites are not causative of the increased heat production.

11. When carbohydrate is converted into fat there is a largely increased elimination of CO_2 without concomitant increase in the metabolism. Therefore an increase in CO_2 production can not be a stimulus to increased heat production.

12. The transmutation of fructose into glucose, presumably through methyl glyoxal, does not increase the metabolism in the dog made diabetic with phlorhizin. The mere presence of unoxidixed intermediary fragments of fructose is therefore without influence upon metabolism.

13. Though there is a reduction of the CO_2 combining power of the blood plasma after the ingestion of hydrochloric acid, it has a very slight effect upon metabolism in comparison with that induced by the administration of glucose.

14. When a dog is caused to run at a rate of 4800 meters or 3 miles per hour, the additional energy production for the unit of work is slightly more without food than when 70 grams of glucose are given. The influx of glucose molecules is immediately used in the production of work. There is no excess of metabolites with which to raise the metabolism to a higher level and the intermediary metabolites of glucose, though formed in largely increased measure, exert no specific power to raise the level of that basic metabolism upon which the definite quota of energy necessary to accomplish work is superimposed.

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B. Conclusion

One can not escape the conclusion that in the presence of an abundant quantity of oxidizable fragments of carbohydrate metabolism the heat production is raised to a higher level. Definite affinities for carbohydrate consumption are satisfied which are not involved when the extra supply of glucose is being continually depleted under the influence of work or is reduced, as in fasting, when the blood stream is under the regulatory control of the liver. The production of increased heat after carbohydrate ingestion may be termed the *metabolism of carbohydrate plethora.*

III. THE INFLUENCE OF FAT INGESTION UPON THE HEAT PRODUCTION

In the experiments of Magnus-Levy already cited glucose was given to a dog at the same time as lard and therefore the results obtained are not technically above reproach.

Murlin and Lusk (28) made a study of the behavior of the metabolism of a dog after administering an emulsion of fat and noted also the influence upon the metabolism when fat and glucose were administered together. The results obtained are shown in charts I and II.

It appears that when fat alone is administered the heat production gradually rises until about the sixth hour when it reaches its maximum and then gradually falls until the twelfth hour when the basal level is regained. The maximum level of metabolism is 30 per cent above the basal level. The work of Bloor (8) has shown that after giving fat to a dog there is a gradual rise in the fat content of the blood, the maximum being attained in the sixth hour, after which there is a fall. Here, then, as in the case of glucose ingestion the metabolism is influenced by the mass of metabolites reaching the cells.

The respiratory quotients after giving fat were always lower than the general average of such quotients found in the determinations of the basal metabolism with which they were compared. It was calculated that all the extra heat produced was at the expense of an added increment of oxidized fat.

When the fat emulsion containing 75 grams of fat was given together with a solution of 70 grams of glucose there was a primary increase in the metabolism due to the combustion of glucose, as indicated

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by high respiratory quotients, and this state was followed by a continuance of the high level of metabolism with a fall in the respiratory

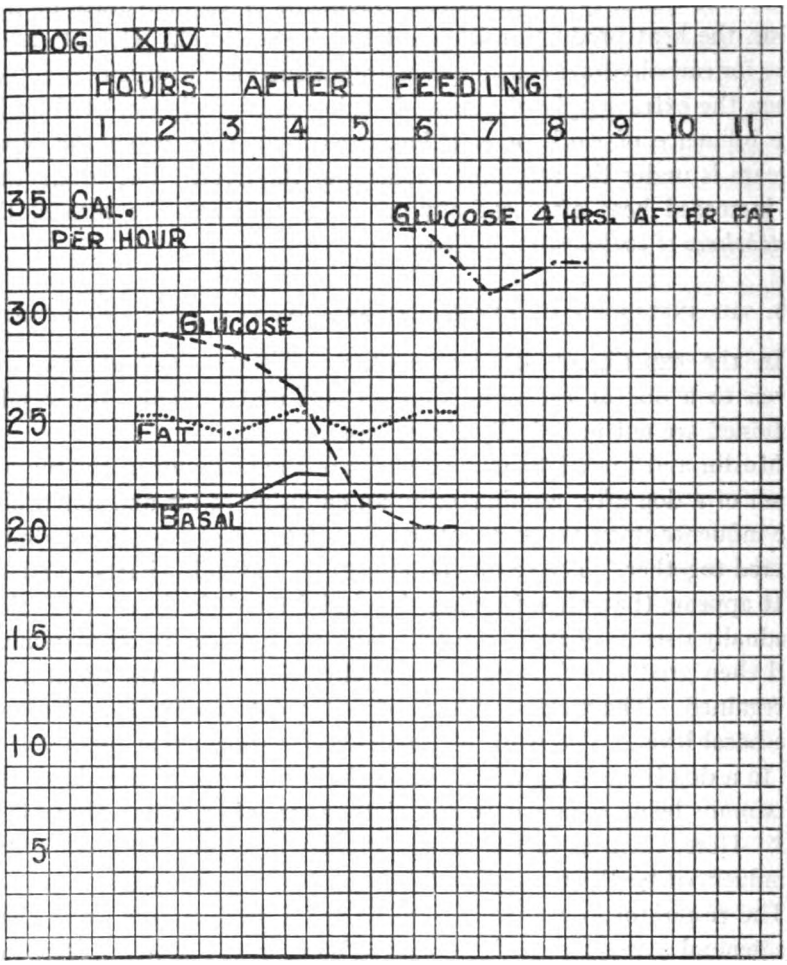

CHART I. THE EFFECT OF FAT, OF GLUCOSE, AND OF GLUCOSE PLUS FAT UPON THE HEAT PRODUCTION (28)

quotients due to the subsequent absorption and combustion of fat. This is the reason why a mixed diet of fat and carbohydrate is satisfying for a longer period than when carbohydrate alone is taken.

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The glucose is given four hours after the ingestion of fat, so that the maximum effect of glucose falls at the same time as the maximum

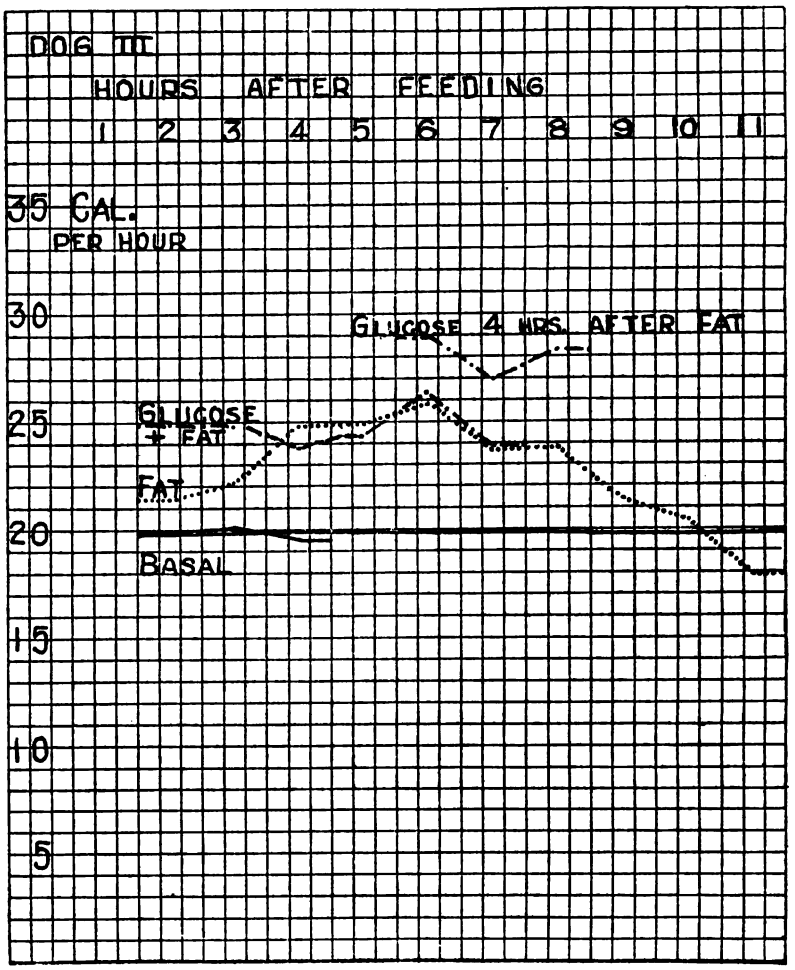

CHART II. THE EFFECT OF FAT AND OF GLUCOSE PLUS FAT UPON THE HEAT PRODUCTION (28)

effect of fat, the resulting increase in the heat production is equal to the sum of the increases which each substance given alone would have induced. This appears as follows:

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	R. Q.	CALORIES PER HOUR	INCREASE ABOVE NORMAL	
			Calories	Per cent
Basal	0.85	21.5		
Fat, 75 grams	0.80	25.0	3.5	16
Glucose, 70 grams	1.00	28.6	7.1	33
Glucose 70 grams, four hours after fat, 75 grams	0.93	32.3	10.8	50

It is evident that when carbohydrate is given at the height of fat ingestion, the respiratory quotient is lower than unity and betokens the coincident oxidation of fat and carbohydrate Therefore when these two materials are transmitted through the blood stream together there is a direct summation of effect. Since the metabolism of glucose is at a maximum when 70 grams are given, it follows that for the utilization of fat an entirely different mechanism is invoked. There must be definite individual affinities within the cell which utilize fat metabolites when transported to them in the blood stream.

A question of some difficulty arises at this point. Why should not the fat formed synthetically after glucose ingestion be immediately oxidized as is ingested fat when given with glucose? One can explain this only on the assumption that the synthesis of fat from carbohydrate is limited to a restricted area or locality of body tissue, whereas the oxidation of carbohydrate and of fat is a property common to all tissue. The localized production of fat from carbohydrate is indicated by the fact that, whereas the theoretical respiratory quotient for this reaction is 8.0, the actual quotient obtained from an entire animal after stuffing it with carbohydrate rarely exceeds 1.30.

According to the well-known experiments of Knoop (18), fatty acids are oxidized on the β-carbon atom, yielding successively two carbon atom chains. The oxidation of caproic acid would follow the course shown by formula on following page.

If palmitic acid broke up by successive oxidation into acetic acid the following equation would represent its transformation:

$$\underset{\text{Palmitic acid}}{C_{16}H_{32}O_2} + 14\,O = \underset{\text{Acetic acid}}{8C_2H_4O_2}$$

1 gram = 1.348 grams
9.353 calories = 4.706 calories

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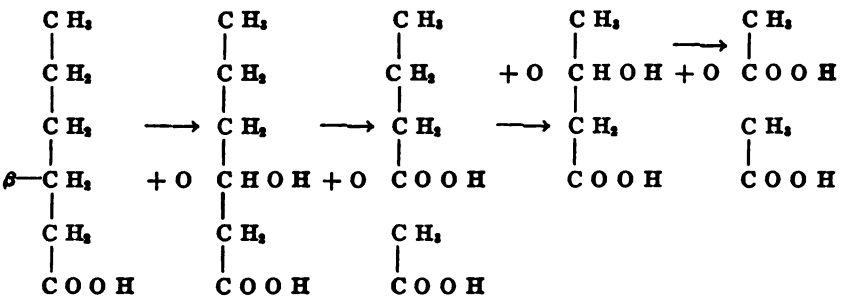
This reaction involves a loss of heat of 50 per cent. There is nothing to indicate that the energy evolved in the oxidative transformation of palmitic acid is physiologically distinct from that produced in the oxidation of acetic acid itself. The whole of the oxidation process may be affected through the mechanism of a single affinity of the cell.



Recently performed and still unpublished experiments done in my laboratory show that when acetic acid is given with glucose there is an increase in metabolism equal to that produced by the individual substances acting severally. This supports the theory of its being an intermediary metabolite of fat. Acetic acid is quickly absorbed and must be immediately oxidized after absorption, for it exerts no influence upon the CO_2 combining power of the blood.

The results may be thus expressed:

	INCREASE ABOVE BASAL METABOLISM	
	Calories	Per cent
Glucose, 58 grams	+4.71	+27
Acetic acid, 3 grams	+3.13	+18
Sum of both	+7.84	+45
Glucose, 50 grams + acetic acid, 3 grams	+7.23	+41

Diabetic acidosis has its origin from β-hydroxybutyric acid when it is retained in the body as an unoxidized residuum of fat metabolism.

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If the condition of acidosis were determinative of a higher level of metabolism after fat ingestion, one would expect that the height of metabolism in diabetes would be proportional to the height of the acidosis. However, in an analysis of 23 cases of diabetes, Allen and Du Bois (1) found that no relation existed between the intensity of acidosis and the height of the metabolism. The patient who had the highest metabolism showed very slight acidosis.

It has already been stated that the energy required to move a running dog was the same per horizontal kilogram meter, whether the energy were obtained from ingested glucose or from the dog's own body fat after the dog had fasted thirteen days. Furthermore, the basal metabolism of this dog was the same on the fifteenth day of fasting when the respiratory quotient was 0.73 as it was after two days of a carbohydrate-containing diet, at which later date the respiratory quotient was found to be 0.93. As sources of energy for the basic needs of the body fat and carbohydrate are therefore mutually interchangeable according to the law of isodynamic equivalents. It is only when the concentration of either or both rises high in the nutrient fluid that the special separate affinities come into play and cause or enable the metabolism to reach higher levels.

The influence of fat ingestion upon the metabolism has been more rigorously investigated than the influence of carbohydrate and of protein have been.

A. Summary

1. The heat production in the dog after giving fat gradually rises to a maximum in the sixth hour, when the increase above the basal level may amount to 30 per cent. It then gradually falls and reaches the basal level in twelve hours after its administration. The sixth hour is the time of the maximum fat content of the blood (Bloor).

2. The additional heat produced is at the expense of the oxidation of fat.

3. When glucose and fat are given together the former is first oxidized, the heat production rises and the respiratory quotient approximates unity; the level of increased heat production continues through subsequent hours on account of the absorption of fat, the respiratory quotient falling on account of the increased oxidation of the latter substance.

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4. When glucose is given four hours after the ingestion of fat so that the maximum effect of glucose ingestion falls at the time of the maximum metabolism induced by fat, there is a summation of effect, the heat production reaching a level above that of the basal metabolism by the sum of the two several increments which each substance would have produced. The respiratory quotient indicates the metabolism of fat as well as carbohydrate.

5. If glucose and acetic acid are administered together the same summation of effect occurs.

6. Hence, in the presence of an amplitude of fat and of glucose molecules, the affinities entering into the mechanism of the increased destruction of either appear to be separate and different.

7. The reason why fat, which is synthetically produced from carbohydrate, is not oxidized as is fat when ingested with carbohydrate, may possibly be that the production of fat from carbohydrate may be limited to a restricted area or locality of tissue, whereas the oxidation of carbohydrate or of fat is a property of all tissues.

8. The basal metabolism is independent of the height of the respiratory quotient, and therefore the basic requirement may be supported by isodynamic equivalents of fat or carbohydrate.

9. The severity of diabetic acidosis is no criterion of the height of the metabolism in diabetes.

B. Conclusion

The same conclusion is reached regarding fat as regarding carbohydrate, that in the presence of an amplitude of fat particles there is a *metabolism of fat plethora*, due to the utilization of fat by special fat receptive cellular affinities.

IV. THE INFLUENCE OF PROTEIN UPON THE HEAT PRODUCTION

The general conclusions reached by Rubner as regards the influence of protein ingestion upon the heat production have been set forth in the introduction. It should be recalled that when Rubner wrote his book, "Die Energiesetze," in 1902 it was still permissible to consider the protein molecule as a complex containing a glucose radicle. It was not until later that the conception of protein as consisting of

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a chain of amino-acids came to be generally accepted. At the present time one must not only consider the effect upon metabolism of the ingestion of meat, but also the behavior of the individual metabolites into which the protein may be resolved. The story might be spun into a tale of considerable length, but it may be well here to emphasize only the more significant points.

After giving 1200 grams of meat to a dog weighing 13.5 kgm. Williams, Riche and Lusk (43) determined the hourly heat production by both direct and indirect calorimetry. The results are presented in the accompanying diagram (chart III). The basal metabolism measured 22.3 calories but after giving meat it rose to a height of 36 calories in the second hour and to 42 calories in the third hour, a maximum increase above the basal of 88 per cent. The heat production was maintained at a level above 40 calories through the tenth hour. In the fourteenth hour it had fallen to 37 calories and then remained at 30 calories up to the eighteenth hour, falling rapidly to 25 calories in the twenty-first hour.

Except in the earlier hours of the experiment the curve of urinary nitrogen elimination is quite parallel to the heat production. The small elimination of urinary nitrogen in the early hours is due to the accumulation of urea within the blood and tissues and not to a much lower protein metabolism.

During ten hours of the experiment the quantity of carbon eliminated in the respiration was less than the amount which would have been so eliminated had the protein metabolized, as measured by the nitrogen in the urine, been wholly oxidized. This carbon retention amounted to the equivalent of a retention of 34.5 grams of glucose. Calculated on the presumption of this retention of glycogen from the protein metabolism of the period, the oxygen absorption should have been 184.55 grams. Actually consumed, there were 186.2 grams of oxygen. If carbon had been retained as fat only 169.7 grams of oxygen would have been required. It is therefore apparent that glucose may be formed normally from protein and not merely in diabetes as a pathological by-product.

As a second illustration of this phenomenon, McCann (24) has shown that the administration of the protein of meat to a normal man on the eleventh day of fasting resulted in the initial establishment

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of respiratory quotients of 0.68 in two successive hourly periods. The quotients betoken the retention as glycogen of the whole of the glucose formed from protein, for they are quotients hitherto obtained

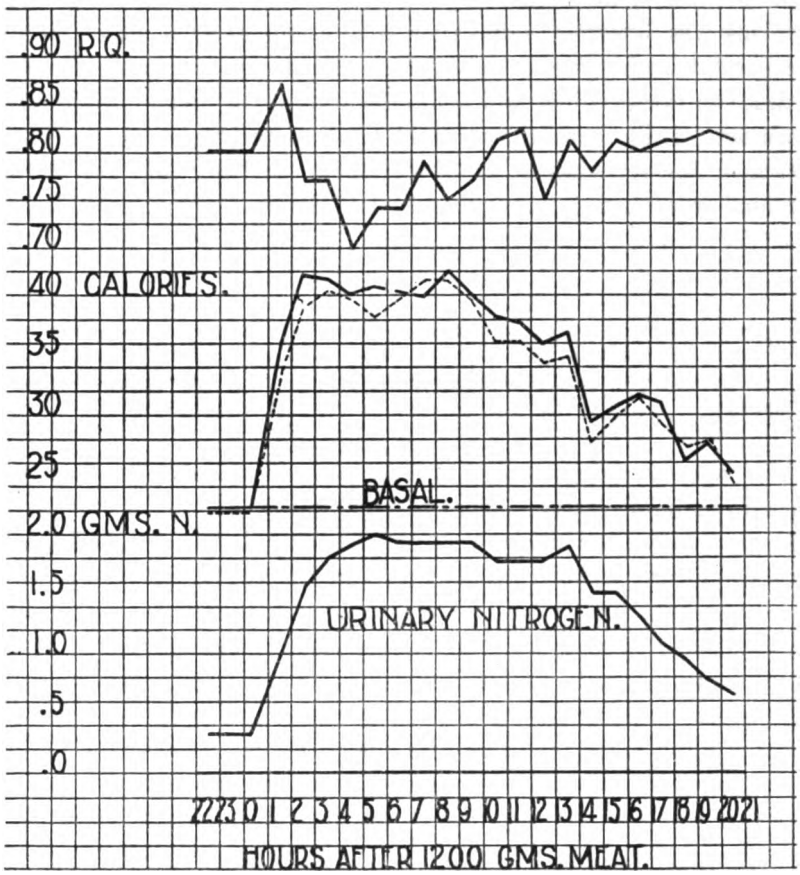

CHART III. SHOWING THE RESPIRATORY QUOTIENT

The total metabolism by indirect calorimetry (solid line), by direct calorimetry (dotted line) and the nitrogen elimination during hourly periods after the ingestion of 1200 grams of meat by a dog (43).

only in severe diabetes under circumstances in which the sugar derived from protein was not oxidized but was eliminated in the urine. The greedy cells of the fasting body laid hold of the sugar produced from protein and deposited it as glycogen.

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It has already been shown that the deposition of glycogen is effected without increasing the heat production.

Conditions, however, may be such that fat also may arise from protein. Thus, in certain experiments (23a) the basal metabolism of a dog was determined and then 1000 grams of meat were given in the early morning, the standard diet containing 75 grams of carbohydrate in the evening, and again 1000 grams of meat the following morning. These conditions would tend to produce glycogen saturation of the repositories for glycogen in the body and the carbon retained from protein might then be laid down in the form of fat, as is set forth in the following analysis:

	INDIRECT	DIRECT
Basal metabolism per hour	14.25	14.31
1000 grams meat, average fifth, sixth, seventh hours	27.55	28.44
Increase	93 per cent	

The respiratory quotients of the retained pabulum were calculated to be 0.708, 0.688, 0.685, betokening a deposit of fat. Had the 0.84 gram carbon, which was retained hourly, been deposited in the form of glucose, indirect calculation would have shown 30.30 calories to be the heat production. The evidence is therefore that protein carbon can be synthesized both into glucose or into fat and retained in the body as such. It has been shown that the production of fat from glucose takes place with the formation of but little extra heat liberation and here the same process must prevail.

Following the ingestion of 1000 grams of meat given to the animal mentioned above, the respiration rate rose from a basal level of 7½ per minute to 23½ per minute, the animal resting quietly throughout.

A great increase in the heat production may also be observed in man after taking meat in large quantity, though the rise is not as great as in the dog. A dog weighing 10 kgm. may devour 1000 grams of chopped meat within a minute, whereas it requires about half an hour or more for a man to take 660 grams of the same material. In the dog the protein metabolized may be of greater energy value than the total heat production, whereas in man only a fraction of the total heat production will be derived from the meat ingested. The follow-

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ing chart (chart IV), showing the influence of the ingestion of 660 grams of meat by (1) a normal man, (2) an achondroplastic dwarf, and (3) a legless man, is taken from the work of Aub and Du Bois (4).

It appears that the sulphur elimination precedes that of nitrogen, illustrating the presence of a lag in nitrogen elimination. In the achondroplastic dwarf there is a maximal increase in the heat production of 46 per cent above the basal level. This increase is not relatively as large as in the dog, but the difference observed is probably due to the limitations of the digestive tract. The dog mentioned in the last experiment would never partake of more than 1200 grams of meat at one time, and the upper limit of metabolism must have been nearly or quite reached in the case described.

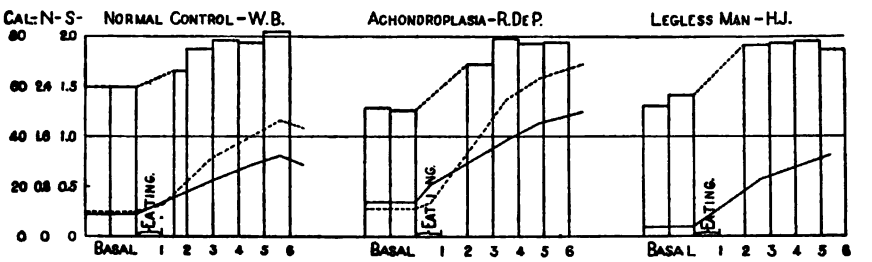

CHART IV. ILLUSTRATING THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN MAN

The columns show the basal heat production in calories per hour rising after the subject has eaten meat containing 23 to 25 grams of nitrogen. The dotted line represents the excretion of sulphur in the urine in decigrams, the continued line, the nitrogen elimination in grams per hour (4).

Whereas, as in the dog, it was noted that after giving meat the increase in heat production might amount to 50 per cent of the calories of the extra protein metabolized, in man it was discovered that fully 75 per cent of the energy content of the extra protein metabolized reappeared in the form of the heat of specific dynamic action. It is obvious that a meat diet is physiologically wasteful.

In the achondroplastic dwarf, with large body and short legs, and in the legless man the specific dynamic effect of protein was more in evidence than in the normal controls. Possibly this may have been due to the fact that in the former individuals the liver or some other organ or organs bore a greater proportion to the total weight than normally, and this suggests the possibility that the seat of the

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"specific dynamic action" of protein may reside in the liver or some other organ or organs in greater degree than in the muscles.

However, Aub and Means (4a) find that the response of the human organism to the specific dynamic action of meat is just as great in severe cirrhosis of the liver as in the normal condition. They conclude that the liver is not the main site of the specific dynamic action or that it can adequately perform that function even in disease.

The increase in the heat production after protein ingestion greatly transcends that which follows the giving of carbohydrate and fat, and it is of a different character.

One sharply characteristic quality of the specific dynamic action of protein is that when once the level of heat production is increased after giving meat any energy necessary for the production of work is superimposed upon this higher level of metabolism. This was first demonstrated by Rubner (37) in man and may be recorded as follows:

	CALORIES	
	Per day	Increase due to work
No food, rest	1976	
Cane-sugar, 600 grams, + H_2O, 3000 grams, rest	2023	
Same + work (100,000 kgm)	2868	845
Protein, large amount of meat	2515	
Same + work (100,000 kgm)	3770	855

This work was confirmed and extended by Anderson and Lusk (2) and showed that the energy of metabolism was the same when a dog ran 3 miles an hour whether or not glucose had been given in large quantity; also that the energy expenditure required for running was superimposed upon the higher metabolism induced by meat ingestion or by such a fragment of protein metabolism as alanin. This distinction has important theoretical bearing.

Their results may be epitomized as tabulated on following page.

The attractive theory of Rubner is that when protein is metabolized it can be utilized for cell life only in so far as it is convertible into glucose, and that such fragments as are not so converted are oxidized with the production of free heat which is of as little value for the maintenance of the living mechanism as heat produced in the

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body through high powered electric currents, for example. The latter form of heat does not alter the fundamental metabolism.

This theory lent itself to experimental proof for Ringer and Lusk (32) found that, whereas glycocoll and alanin were completely converted into glucose in the organism of the diabetic dog, only three of the five and four carbon atoms contained respectively in glutamic and aspartic acids were convertible into glucose.

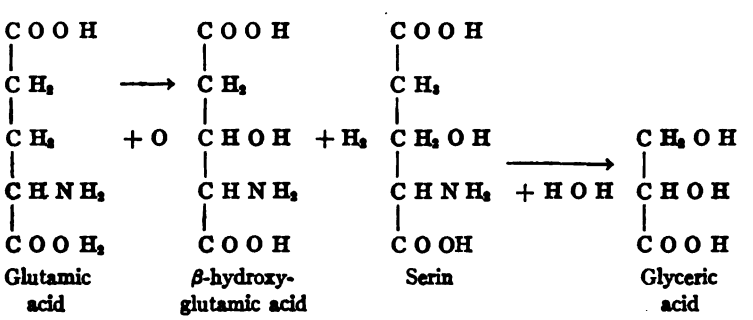
	CALORIES PER HOUR	R. Q.	DISTANCE IN METERS	WORK IN KILOGRAMS TO MOVE 1 KGM. 1 METER
No food, rest	17.2	0.86		
No food, work	76.1	0.79	4806	0.578
Glucose, 70 grams, rest	21.0	1.07		
Glucose, 70 grams, work	77.1	0.92	4771	0.555
Meat, 750 grams, rest	70.0	0.80		
Meat, 750 grams, work	92.4	0.80	4704	0.587*
Alanin, 20 grams, rest	21.0	0.84		
Alanin, 20 grams, work	82.0	0.78	4777	0.583†

* Corrected for influence of meat.

† Corrected for influence of alanin.

Ringer and Lusk suggested that glutamic acid might be oxidized on its β-carbon atom which on cleavage might yield serin, the latter being converted into glyceric acid on deamination. Glyceric acid, when given to the diabetic dog, was converted into glucose. Recently Dakin (9) has isolated a new amino-acid, β-hydroxyglutamic acid from caseinogen, and has also produced it synthetically. This acid, he finds, yields glucose to the extent of three of its carbon atoms when it is given to the diabetic dog.

Perhaps the transformation of glutamic acid proceeds as follows:



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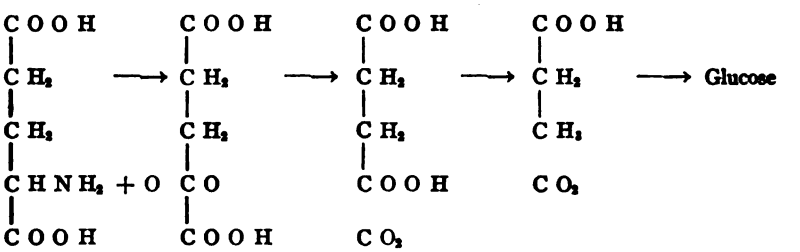
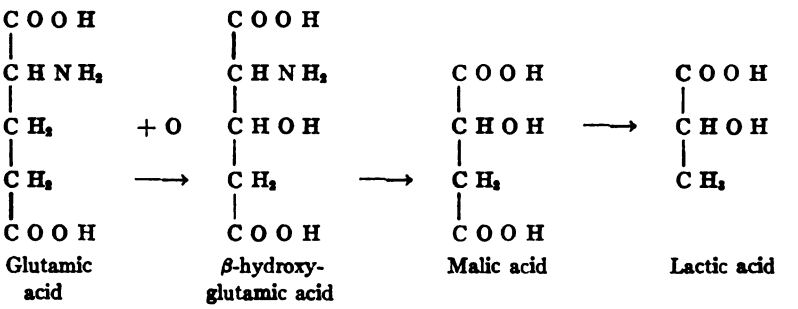
Or since yeast cells may convert glutamic acid into ketoglutaric acid (29) and this again into succinic acid (11) and, since succinic acid if fed to the phlorhizinized dog, is convertible into glucose, (31a) the following intermediary reactions constitute a second possibility:



Dakin (9) believes that the metabolism of glutamic acid probably takes place through malic acid as an intermediate metabolite. Ringer, Frankel and Jones (31a) have shown that malic acid is convertible into glucose. Dakin's suggestion follows the formulae:



Whatever the intermediary reactions, the energy relations may be written as follows:

$$2C_6H_9NO_2 + 3H_2O + 3O_2 = C_6H_{12}O_6 + CN_2H_4O + 3H_2O + 3CO_2$$

Glutamic acid	Glucose	Urea
1 gram	= 0.612 gram	+ 0.204 gram
3.662 calories	= 2.298 calories	+ 0.516 calory

This reaction is therefore exothermic, 3.662 calories in glutamic acid yielding 2.298 calories in glucose, 0.516 calories in urea and 0.848 calories in the intermediary oxidative processes. The physio-

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logically available calories in glutamic acid are 3.662 minus 0.516 contained in urea, or 3.146 per gram. Hence, in calculating the calories available one would say that 73 per cent of the total passed through the glucose stage and 27 per cent passed through other oxidative channels

If Rubner's theory (see p. 000) of specific dynamic action were correct, then glutamic acid would furnish energy to the cells in so far as it was convertible into glucose, whereas the rest of the energy content would be liberated as free heat. Its specific dynamic action could be measured as 27 per cent, which almost coincides with the figure 30 per cent, as given by Rubner. Since the protein of meat yields 22 per cent of glutamic acid and that of gliadin nearly 50 per cent (Osborne), it follows that an important fragment of protein metabolism is represented in this amino-acid.

However, it has been discovered that the ingestion of 20 grams of glutamic acid by a dog gives absolutely no specific dynamic action (22) and this is also true of its hypothetical cleavage product, succinic acid (3). The demonstration that glutamic acid exerted no specific dynamic action after its ingestion is a proof that the process of deamination and urea production have no influence upon the heat production.

It has furthermore been shown that aspartic acid, $HOO\text{-}CCH_2\text{-}CHNH_2\text{-}COOH$, exerts no specific dynamic action (3) and this further substantiates the above conclusions.

Other experiments showed that neither 20 grams of leucine nor 20 grams of tyrosine caused any conspicuous rise in metabolism after their ingestion (22), although tyrosine at least would present a multitudinous array of oxidative products.

It was only when two amino-acids which are completely converted into glucose by the diabetic organism were given, that the heat production of a normal dog was very greatly increased. These two amino-acids are glycocoll and alanin. Serin has never been tested but would probably behave like alanin. These experiments overthrow the validity of Rubner's theory of the specific dynamic action of protein.

In one experiment 20 grams of glycocoll were given to a dog and the metabolism rose 33.7 per cent above the basal level. The 20 grams of glycocoll contained 42 physiologically available calories of

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which 34 calories or 81 per cent were available for metabolism between the second to the seventh hours in the calorimeter experiment after giving the substance. Since the heat production was increased by 33.75 calories, or by 80 per cent of the calories in the ingested substance, it is evident that the extra heat production after giving glycocoll may equal the entire energy which can be furnished by the metabolism of glycocoll itself.

This at once raises the question: Is the energy in glycocoll merely freed and given off without affecting the basal metabolism? Does it merely explode with a puff?

If one writes the reaction and the energy involved in the conversion of glycocoll into glucose and urea the following equation results:

$$6C_2H_5NO_2 + 3CO_2 + 3H_2O = 2C_6H_{12}O_6 + 3CH_4N_2O + 3O_2$$

Glycocoll	Glucose	Urea	Oxygen
20 grams	16 grams	8 grams	4.26 grams
62.2 cals.	60.08	20.22	14.0 as oxidized fat

According to this equation 62.2 calories in glycocoll become converted into glucose and urea, containing together 80.3 calories with the intermediary liberation of a compound yielding oxygen in such quantity that it can effect the oxidation of an amount of fat which can produce 14 calories. The reaction would therefore be rewritten as follows:

Glycocoll + fat + CO_2 + H_2O = Glucose + CH_4N_2O + CO_2 + H_2O
20 grams = 16 gm. + 8 gm.
62.2 cals. + 14 cals. = 60.08 cals. + 20.22 cals.

Hence, material containing 76.2 calories is converted into material containing 80.3 calories. The reaction is still *endothermic*.

When, however, glycocoll is given to a dog diabetic with phlorhizin the heat production is very greatly increased, far beyond the requirement of satisfying this endothermic quota of energy.

See following table for the results.

The extra calories produced over and above the basal metabolism for four hours amounted to 25.9 calories, which corresponds with 24.5 extra calories produced in the same dog when he was normal in the experiment already described.

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Dog III, March 25, 1915, Experiment 104. Basal phlorhizin metabolism as affected by 20 grams of glycocoll in 210 cc. of water at 38° plus 1 gram of Liebig's extract

HOURS		R. Q.	CALORIES	
			Indirect	Direct
1	Basal	0.733	23.78	24.53
2	Basal	0.716	23.82	23.84
	Average	0.724	23.80	24.18
3	Glycocoll, 20 grams			
4	Glycocoll, 20 grams	0.707	34.21	32.34
5	Glycocoll, 20 grams	0.745	31.65	29.47
6	Glycocoll, 20 grams	0.700	29.24	30.07
7	Glycocoll, 20 grams	0.702	25.99	26.85
	Average	0.720	30.27	29.38

This is the *experimentum crusis* which demonstrates that the specific dynamic action of glycocoll is independent of its oxidation. Rather, there must be chemical intermediates produced which act upon the protoplasm of the cells, lifting them to a higher level of metabolism without it being necessary that they themselves furnish the energy of metabolism. I have therefore spoken of this condition as the *metabolism of amino-acid stimulation*. This does not necessarily mean that acid is actually liberated.

To investigate this point I have given to a dog 9.6 grams of glycocoll neutralized with 10 grams of sodium bicarbonate and have witnessed the heat production increase 5.2 calories per hour during the second and third hours. The bicarbonate given alone was without influence. When 7.6 grams of glycocoll acid were given the heat production rose 1.6 calories per hour and when 10 grams of glycollate of sodium were ingested a rise of only 1.2 calories was recorded. The administration of glycollic acid greatly reduced the carbon dioxide combining power of the blood, which testifies to its slow oxidation.

It would seem likely that glycollic acid would be the first intermediate product of glycocoll deamination, as follows:

$$\begin{array}{l} CH_2NH_2 \\ | \\ COOH \end{array} + HOH \longrightarrow \begin{array}{l} CH_2OH \\ | \\ COOH \end{array} + NH_3$$

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However, glycollic acid is not convertible into glucose in the organism. It may be, however, that the reduction of the acid group takes place before or simultaneously with the deamination process and glycolaldehyde is generated, which substance it has been shown is convertible into glucose (39). If so, the stimulation of cellular metabolism probably occurs before this step because the synthetic production of glycogen does not involve a stimulation to increased heat production.

The experiments may possibly be explained after another fashion. It may be that the amino-acid is greedily absorbed by the cell and that the alkali neutralizing it is not. Under these circumstances the liberation of free acid may possibly be the stimulus which increases cellular metabolism. Under this hypothesis the cell membrane would be largely impermeable to the sodium salt of glycollic acid present in the blood after the ingestion of either the acid itself or glycollate of sodium and little result would be noticed in the way of cellular stimulation.

When glycocoll is given the extra heat production is proportional to the quantity ingested; that is to say, it is proportional to the intensity of the chemical stimulus.

When glycocoll is administered with glucose the extra heat production is the equivalent of the sum of the extra quantities of heat which either substance would have induced alone. Furthermore, when glucose and glycocoll are given at the height of fat ingestion the extra heat production rises to a level which is the equivalent of the influences exerted by the substances as individuals. This is seen in chart V and may be illustrated in the following table:

	HOURLY INCREASE IN CALORIES ABOVE BASAL	PER CENT
Glycocoll, 20 grams	4.9	25
Glucose, 70 grams	6.9	30
Fat, 75 grams	3.9	17
Sum of all	15.7	72
Glycocoll, 20 grams + glucose, 50 grams 4 hours after fat, 75 grams.	14.6	64

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It is obvious that glycocoll, which is completely convertible into glucose, does not behave like glucose (1) in substituting its energy for the energy of glucose in metabolism; (2) in being passively elimi-

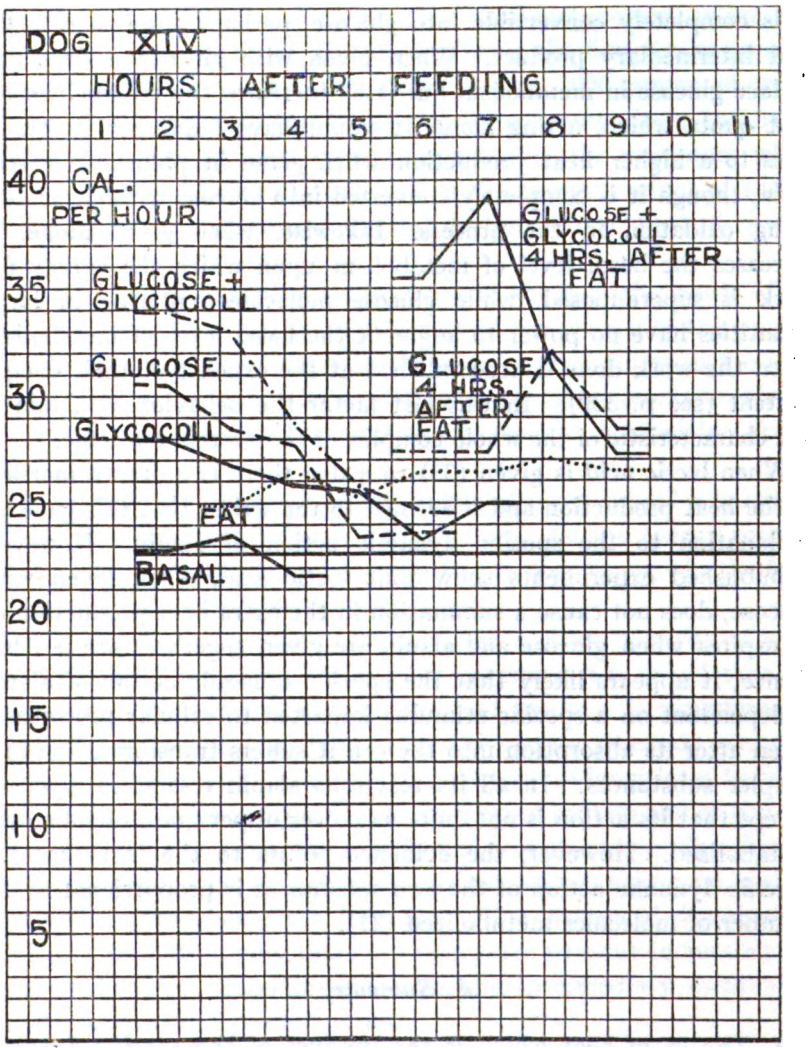

CHART V. THE EFFECT OF FAT, OF GLYCOCOLL, OF GLUCOSE, OF GLUCOSE PLUS GLYCOCOLL, AND OF GLUCOSE PLUS GLYCOCOLL PLUS FAT UPON THE HEAT PRODUCTION (28)

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nated as glucose in the urine of the diabetic dog, It follows, also, that ingested glucose can not synthetically form glycocoll under normal conditions.

The behavior of alanin is in every way similar to that of glycocoll. It is completely convertible into glucose, perhaps through a lactic acid intermediary product. When given with glucose it does not replace glucose in metabolism but itself increases the metabolism by that quota which, acting alone, it would have induced. It stimulates to a higher heat production when given in phlorhizin glycosuria, though it is completely converted into glucose without undergoing oxidation in the process. Likewise, when given alone, it increases the basal level of metabolism upon which the energy for work is superimposed, while glucose molecules entering in large quantities have no power to augment the basal level of metabolism when the work done is accomplished at the expense of their energy content (see p. 330). In this last factor the behavior of alanin is but characteristic of the whole complex of the protein molecule.

When lactic acid is given (33) to a dog there is quite an increase in the heat production and it seemed to the writer that this gave an explanation to the specific dynamic action of alanin. However, unpublished experiments show that lactic acid, when given with glucose, does not cause a summation in the extra heat production as transpires when glucose and alanin are given together (see p. 326). Hence, it appears likely that the specific dynamic action of alanin is dependent on a specific stimulus imparted to cellular protoplasm when after its absorption into the cell it suffers transformation into simpler substances. In all its reactions alanin resembles glycocoll except that its action is not quite as powerful per gram of substance metabolized. However, the evidence points to the fact that the specific dynamic action of the two substances is proportional to the number of molecules metabolized (21).

A. Summary

1. The extra heat which is the product of the specific dynamic action of protein may be used in substitution for the extra heat induced by the effect of environmental cold (Rubner).

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2. The increase in heat production is proportional to the protein metabolism of the time. It occurs when endogenous protein metabolism increases as in the case of phlorhizin glycosuria (Rubner).

3. A dog given 1200 grams of meat showed a maximum increase in metabolism of 88 per cent above the basal metabolism, an increase which remained nearly at this height during the first ten hours after meat ingestion. Another dog, after taking 1000 grams of meat, showed an increase in metabolism of 93 per cent above the basal. These quantities of meat were approximately the maximum which the dogs would eat. Fifty per cent of the energy content of the increased protein metabolized appears in the form of heat of specific dynamic action.

4. When meat is thus given in excess of the nutritive needs of the cell there may be a retention of a part of the energy of the protein metabolized, deposited either in the form of glycogen or in the form of fat, depending upon the condition of the glycogen reservoirs of the body. Neither of these processes involves an appreciable liberation of energy.

5. In man the ingestion of 660 grams of meat caused a maximal rise in the basal metabolism of 46 per cent. Of the energy content of the increased protein metabolized 75 per cent appears in the form of the heat of the specific dynamic action.

6. If the energy required to accomplish a given quantity of work be determined before and after meat ingestion it is found that the energy requirement for work in the first instance is superimposed upon the metabolism as induced by the specific dynamic action of protein in the second instance. This strictly differentiates between the character of the specific dynamic action of protein and of glucose. In this regard alanin behaves exactly like protein and not like glucose.

7. Glutamic acid with its five carbon atoms exerts no specific dynamic action when given to a dog. The process of deamination and urea formation may therefore take place without increasing the heat production. Succinic acid, a possible intermediary metabolite, exerts no specific dynamic action.

8. Aspartic acid behaves like glutamic acid.

9. Neither leucin nor tyrosin cause a conspicuous rise in metabolism.

10. Administration of 20 grams of glycocoll to a normal dog causes

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a very great increase in the heat production. The quantity of extra heat produced (25.9 calories in four hours) may amount to the entire energy of the glycocoll metabolized during the period.

11. When 20 grams of glycocoll were given to a dog diabetic with phlorhizin the quantity of extra heat produced in four hours (24.5 calories) was exactly the same as when the material was given to the same animal when normal in spite of the fact that the ingested glycocoll is completely converted into glucose and urea without oxidation. Therefore, some intermediary metabolites act as chemical stimuli to metabolism (Experimentum crucis).

12. Glycocoll neutralized with sodium bicarbonate has the same influence upon the heat production as when given alone. The bicarbonate given alone is without influence upon the metabolism.

13. Glycollic acid and sodium glycollate have little influence upon the heat production. It is indicated that glycollic acid may not be as readily permeable to cell membranes as is the readily diffusible glycocoll.

14. When glucose is given with glycocoll or when the two combined are given at the height of fat metabolism, the total specific dynamic action of the mixture is equal to the sum of those quantities of extra heat production which each substance acting separately would have induced. The calories of glycocoll can not, therefore, be substituted for the calories of glucose.

15. The behavior of alanin is analogous to that of glycocoll. Molecule for molecule, it exerts the same specific dynamic effect.

B. Conclusion

The specific dynamic action of protein consists in a specific chemical stimulus of the cellular protoplasm, which is independent of the oxidation of the material through which the stimulus is applied. It may be termed the *metabolism of amino-acid stimulation.*

V. A THEORY OF METABOLISM

It may be well to restate a theory of metabolism already advanced (23a) which is a modified form of one enunciated by Rubner (38).

One may conclude that the influence of food ingestion upon the

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basal metabolism of the quiet, resting cell may be upon three independent mechanisms within the cell:

a. A mechanism which is receptive to a chemical stimulus derived from such amino-acids as glycocoll and alanin.

b. A mechanism of carbohydrate plethora which allows the metabolism of carbohydrate up to the limits imposed by "self regulation."

c. A mechanism capable of receiving power from that quota of fat which, when in excess, increases the heat production of the cell.

REFERENCES

(1) ALLEN, F. M., AND DU BOIS, E. F.: Archives of Internal Medicine, 1916, xvii, 1010.
(2) ANDERSON, R. J., AND LUSK, G.: Journal of Biological Chemistry, 1917, xxxii, 421.
(3) ATKINSON, H. V., AND LUSK, G.: Journal of Biological Chemistry, 1918, xxxvi, 415.
(4) AUB, J. C., AND DU BOIS, E. F.: Archives of Internal Medicine, 1917, xix, 840.
(4a) AUB, J. C., AND MEANS, J. H.: Archives of Internal Medicine, 1921, xxviii, 173.
(5) BENEDICT, F. G.: Transactions of the 15th International Congress of Hygiene, 1912 II, 394.
(6) BENEDICT, F. G., AND EMMES, L. E.: American Journal of Physiology, 1912, xxx, 197.
(7) BLEIBTREU, M.: Pflüger's Archiv für die gesammte Physiologie, 1901, lxxxv, 345.
(8) BLOOR, W. R.: Journal of Biological Chemistry, 1914, xix, 1.
(9) DAKIN, H. D.: Biochomical Journal, 1919, xiii, 398.
(10) DAKIN, H. D., AND DUDLEY, H. W.: Journal of Biological Chemistry, 1913, xiv, 155; xv, 127.
(11) EHRLICH, F.: Biochemische Zeitschrift, 1909, xviii, 391.
(12) FALTA, W.: Deutsches Archiv für klinische Medicin, 1918, cxxv, 233; cxxiv, 1.
(13) FISHER, GERTRUDE, AND WISHART, MARY B.: Journal of Biological Chemistry, 1912-13, xiii, 49.
(14) HENRIOT: Comptes rendus de l'Academie Sciences, 1892, p. 371.
(15) HÖCKENDORF, PAUL: Biochemische Zeitschrift, 1910, xxiii, 281.
(16) HOOBLER, B. R.: American Journal of Diseases of Children, 1913, v, 308; 1915, x, 153.
(17) JOHANSSON, J. E.: Skandinavisches Archiv für Physiologie, 1909, xxi, 1.
(18) KNOOP, F.: Hofmeister's Beiträge zur chemischen Physiologie und Pathologie, 1905, vi, 150.
(19) LEVENE, P. A., AND MEYER, G. M.: Journal of Biological Chemistry, 1914, xvii, 443.
(20) LUSK, G.: Journal of Biological Chemistry, 1912–13, xiii, 27.
(21) LUSK, G.: Journal of Biological Chemistry, 1915, xx, 555.
(22) LUSK, G.: Journal of Biological Chemistry, 1912–13, xiii, 155.
(23) LUSK, G.: Comptes rendus de l' Academie des Sciences, 1919, clxviii, 1012.
(23a) LUSK, G.: Proceedings of the Society for Experimental Biology and Medicine, 1920.
(24) MCCANN, WM. S.: Proceedings of the Society for Experimental Biology and Medicine, 1920.
(25) MAGNUS-LEVY, ADOLPH: Pflüger's Archiv für die gesammte Physiologie, 1894, lv, 103.

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(26) MAGNUS-LEVY, ADOLPH: Archiv für experimentelle pathologie und Pharmakologie, 1899, xlii, 226.
(27) VON MERING UND ZUNTZ, N.: Pflüger's Archiv für die gesammte Physiologie, 1877, xv, 634.
(28) MURLIN, J. R., AND LUSK, G.: Journal of Biological Chemistry, 1915, xxii, 15.
(29) NEUBERG, C., AND RINGER, M.: Biochemische Zeitschrift, 1915, lxxi, 226.
(30) RINGER, A. I.: Journal of Biological Chemistry, 1913, xiv, 43.
(31) RINGER, A. I., FRANKEL, E. M.: Journal of Biological Chemistry, 1913–14, xvi, 563.
(31a) RINGER, A. I., FRANKEL, E. M., AND JONAS, L.: Journal of Biological Chemistry 1913, xiv, 539.
(32) RINGER, A. I., AND LUSK, G.: Zeitschrift für physiologischen Chemie, 1910, lxvi, 106.
(33) RUBNER, M.: Archiv für Physiologie, 1912, Supplement Band.
(34) RUBNER, M.: Sitzungsberichte der königlich preussischen Akademie der Wissenschaften, 1913, viii, 233.
(35) RUBNER, M.: Zeitschrift für Biologie, 1883, xix, 313.
(36) RUBNER, M.: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig, 1902.
(37) RUBNER, M.: Sitzungsberichte der königlich preussischen Akademie der Wissenschaften, 1910, xvi, 316.
(38) RUBNER, M.: Archiv für Hygiene, 1908, lxvi, 15.
(39) SANSUM, W. D., AND WOODYATT, R. T., Journal of Biological Chemistry, 1914, xvii, 521.
(40) SCHWARZ, O., AND PULAY, E.: Zeitschrift für experimentelle Pathologie und Therapy, 1915, xvii, 383.
(40a) STEPP, HERR: Münchener medicinische Wochenschrift, 1920, lxvii, 617.
(41) VOIT, C.: Physiologie des allgemeinen Stoffwechsell und der Ernährung, Handbuch der Physiologie des gesammt-Stoffwechsels und der Fortpflanzung, Leipzig, 1881, pp. 308, 311.
(42) VOIT, C.: Münchener medicinische Wochenschrift, 1902, xlix, 233.
(43) WILLIAMS, H. B., RICHE, J. A., AND LUSK, G.: Journal of Biological Chemistry, 1912, xii, 371.

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HEMOLYTIC JAUNDICE

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INTRODUCTION

Definition

In general, any jaundice may be said to be hemolytic when it is due to increased destruction of the red blood cells, and not to obstruction of the bile passages. A good illustration is afforded by the jaundice which follows the transfusion of blood in cases where there is incompatibility between the patient's blood and that of the donor. Such a jaundice corresponds to the "hematogenous" jaundice of the older writers, a term which is again coming into use since Whipple

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and Hooper (93) have shown that bile pigment may be formed outside of the liver and in the general circulation.

For the purposes of this article however, the term hemolytic jaundice will be restricted to a form of jaundice, usually chronic, in which diminished resistance of the red cells to hypotonic salt solutions is a conspicuous feature, while bile pigment is present in the stools and absent from the urine. Enlargement of the spleen and anemia complete the picture.

The disease occurs in two forms, the congenital and the acquired, the former being by far the commoner. The congenital type belongs to the inheritable diseases, occurring often in several successive generations, occasionally in several members of a family without cases among the ascendants, and also in a strictly congenital form, a single member of a family being affected from birth.

Synonyms

A great variety of names has been employed, according to different conceptions of the nature of the process, viz., chronic acholuric jaundice, chronic infectious jaundice with splenomegaly, chronic familial jaundice or cholemia, hemolytic splenomegaly, hemolytic anemia, and hemolytic jaundice. The last named, however, is the one almost universally used at present.

HISTORICAL

The recognition of the disease is of recent date. Imperfect accounts of the congenital form were given in 1885 by Murchison (65) and in 1890 by Wilson (103), but it was not until 1900 that the first accurate description was published by Minkowski (60). This was soon followed by articles in France by Gilbert, Castaigne and Lereboullet (32), and in England by Barlow and Shaw (4). Ten years later the condition was first recognized in America by Tileston and Griffin (85) and shortly afterwards by Thayer and Morris (83).

The nature of the disease was little understood till 1907, when Chauffard (14) discovered the significant fact that the red cells showed a markedly diminished resistance to hypotonic salt solutions. In the following year he reported (15) the presence of reticulated red cells in large numbers.

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Widal (94) was the first, in 1907, to describe the acquired type in detail and recognize its hemolytic nature, though Hayem (39) had reported similar cases in 1898.

For these reasons the congenital form often is alluded to as the Minkowski-Chauffard type, and the acquired form as that of Hayem-Widal.

TYPES

I. THE CONGENITAL TYPE

The important features are as follows: Jaundice appears either at birth, or during childhood or youth, and persists throughout life. It is usually noted in more than one member of the family, and frequently in two, three, or even four generations. At times, however, though dating from birth, no other members of the family are affected. The icterus is not intense, there are no signs of obstruction of the bile ducts, and symptoms of cholemia, such as itching, bradycardia and xanthomata, are lacking. The urine shows the presence of urobilin, but no bile, while the stools are highly colored, and contain an excess of urobilin. Enlargement of the spleen, which may reach large proportions, is an almost constant feature, while the liver is only slightly or not at all enlarged. A moderate degree of anemia is the rule. The resistance of the red cells to hypotonic salt solutions is diminished, in marked contrast to the increased resistance met with in obstructive jaundice. Reticulated red cells are present in large numbers. The leucocytes may be either normal, increased, or decreased in number.

In spite of the long duration of the disease, the health does not suffer much, and many patients attain an advanced age, death being almost never due to the disease itself. As Chauffard has aptly remarked, the patients are rather jaundiced than sick. Except in a few cases, such as those of Weber (91) and Türk (87), the growth is not interfered with.

In the history a characteristic feature is the occurrence of the so-called "crises;" after an indiscretion of diet, a period of constipation, or without obvious cause, attacks take place in which there is repeated vomiting of bile, often accompanied by fever and pain

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in the region of the spleen or liver. The jaundice deepens during these attacks, the spleen enlarges and if counts are made, it will be found that the red cells have diminished, often with great rapidity. These "crises of deglobulization," as they are termed by the French, occur more frequently in youth, diminishing in number and severity with advancing age.

Between attacks the patient feels fairly well. There is a marked tendency to nose-bleeds during childhood, but hemorrhages from other organs are not met with, an important distinction from Banti's disease and cirrhosis. The enlarged spleen often causes a sense of weight and oppression in the left hypochondrium, and pain may occur in this region, apart from "crises," as a result of perisplenitis.

Etiology

Heredity. The disease is often an exquisitely hereditary affection involving three or even four generations. It is transmitted equally by the male and by the female, and Wilson's (103) statement that it tends to pass from father to daughter, and from mother to son, does not hold good for most instances. The sexes are affected about equally. There seems to be no racial predisposition. Some of the children almost always escape, and the offspring of those who do, remain free from the affection. It has not been found possible to apply the Mendelian laws of the inheritance of dominant and recessive characters.

As in the case of other hereditary diseases, the etiology is obscure. Certain observers, notably Chauffard, attempt to ascribe the disease to hereditary syphilis and to tuberculosis. This seems the more plausible on account of the analogy of hemolytic jaundice with paroxysmal hemoglobinuria, a condition which is usually associated with inherited syphilis.

Chauffard (17) bases his argument on observations on a family in which the usual picture of hemolytic jaundice occurred in twins, the subjects of hereditary syphilis. The father was jaundiced from birth and showed a positive Wassermann reaction. Interesting phenomena were noted after injections of neosalvarsan. In all three splenic "crises" occurred, with pain and increased swelling of the spleen; in one of the twins there had been no previous crises.

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The resistance of the red cells was decreased in two after the injection and increased in the other. The temporary appearance of isolysins was also noted. After a few injections these reactions appeared no longer.

Chauffard regards these phenomena as being in the nature of a Herxheimer reaction, or local reaction in the spleen due to the sudden liberation of toxins from spirochetes which have been killed by the drug. His observations, interesting as they are, cannot be said to prove his point, for he made no control tests on the effect of salvarsan injections in cases of hemolytic jaundice without syphilis, or in cases of syphilis without jaundice. Nor have syphilitic lesions ever been demonstrated in the spleen in hemolytic jaundice.

Guizzetti (38) has also reported a family in which hereditary syphilis is supposed to have played a part. Hemolytic jaundice occurred in four generations, and in two cases, brothers, a marked thickening of the frontal bone, claimed to be syphilitic, was found at autopsy. The husband in the first generation was said to have been syphilitic, but his wife, who was his first cousin, also suffered from splenomegaly, so that it is possible that syphilis had nothing to do with the jaundice transmitted to the offspring. It should be noted that in this family the disease ran a severe course, resulting in the early death of several members. Such malignancy has been noted in no other cases in the literature; it seems possible that it was due to the fact that both parents suffered from the disease, or that it was due to the complication with syphilis.

In general, however, the incidence of syphilis in hemolytic jaundice is not greater than in the population at large; thus Giffin (31) reports only one positive Wassermann reaction out of thirteen patients. Moreover, in the cases of the congenital type where active syphilis has existed, the employment of anti-syphilitic treatment has in no single instance resulted in a cure of the jaundice. It seems fair to conclude that syphilis is not of importance in the causation of the disease.

In the case of tuberculosis, the argument is even weaker. Apart from the casual occurrence of tuberculosis in these patients, it rests essentially on the result of tuberculin injections. It is again to Chauffard (17) that we owe observations on this point. In one

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patient jaundice appeared at the age of fifteen during an attack of pleurisy with effusion. (The congenital type not infrequently first becomes manifest at this age after an acute infection.) When seen by Chauffard at the age of thirty there were signs of active tuberculosis at the left apex. An intradermal injection of tuberculin was followed by a marked local reaction, by pain and increased swelling of the spleen and increase in the jaundice. In another case, a man of twenty years, with a history of tuberculous peritonitis in infancy, still more striking events followed the intradermal injection of tuberculin. Besides an intense local reaction, there was fever of several days duration, the spleen doubled in size, the jaundice increased, acute anaemia supervened and the resistance decreased from 0.64 per cent to 0.76 per cent.

Chauffard considers these cases as showing a local reaction of the spleen to tuberculin, which he regards as proof of the tuberculous origin of the disease. According to him, hemolytic jaundice is a symptom, not a disease, with hereditary syphilis and tuberculosis as the most common factors. But as against this theory it may be objected, in the first place, that tuberculosis of the spleen has never been encountered in the numerous specimens examined, and secondly that hemolytic crises have often been reported in the congenital type in connection with acute infections of various sorts. Now a severe tuberculin reaction is certainly analogous to the toxemia produced by the acute infectious diseases. A verdict of "not proven" may therefore be returned in the case of tuberculosis also.

In conclusion it may be stated that the cause of congenital hemolytic jaundice remains to be discovered.

Pathogenesis

Any theory must take into account the increased fragility of the red cells and the splenomegaly. All writers are agreed that the jaundice is of hemolytic origin, as shown by the increased urobilin excretion (one molecule of hemoglobin gives rise to one molecule of bilirubin), the pigmentation of the organs, and probably certain of the blood changes.

Widal and his school believe that the primary factor is the decreased resistance, the abnormally fragile cells being destroyed in great

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numbers by the normal hemolytic processes of the body, and the enlargement of the spleen being "spodogenous," or simply the result of the increased number of red cells destroyed there.

Troisier (86) on the other hand maintains that the primary condition is the formation of a hemolysin which becomes fixed in the red cells and renders them less resistant, and supports his view by the finding of hemolysins and decreased resistance of red cells in the pleural fluid in cases of hemothorax. Widal (97) accepts this view as applied to the acquired type, and believes that hemolysis does not occur in the circulating blood on account of a deficiency of complement.

Banti (2) however, was unable to demonstrate any lack of complement in the serum, and states that other observers have failed to find increased fragility in red cells that have fixed hemolysin. He believes that the primary fault lies in the spleen, and that hemolysins are produced in this organ in hemolytic jaudice. He states that he was able to reproduce the disease experimentally by the injection of hemolytic sera, observing after a single injection progressive anemia, with similar blood changes and decreased resistance. Both in normal animals and in those who had received injections, he observed that the splenic vein contained more hemoglobin in the serum than was found in other parts of the body, and that the fragility of the red corpuscles was also greater in the splenic vein. Two cases of splenectomy for hemolytic jaundice in man are said to have shown greater fragility in the splenic venous blood than in the peripheral circulation. He concludes that the spleen has an important hemolytic function and diminishes the resistance of the red cells which pass through it.

Banti believes that the pathogenesis of the disease in man is identical with that of his experimental anemia following injections of hemolytic sera, and assumes in the human disease the presence of substances, as yet unknown, which act on the spleen and cause it to produce hemolysins in excess.

Pearce (70, page 93), however, working with normal dogs, was unable to find any free hemoglobin in the serum of the splenic vein, and concludes that Banti's results were due to faulty technique. He found the resistance of the red cells usually the same in the splenic vein and in the artery, and only occasionally slightly less in the vein.

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Since the corpuscles in the femoral vein were also at times less resistant he asks if the changes which have been found in the splenic vein are not those of venous blood in general.

In this connection the experimental studies of Joannovics and Pick (43) on toluylendiamin poisoning in dogs are of interest. They attempted to explain the fact that this substance is hemolytic *in vivo* but not *in vitro*. Following the lead offered by Faust and Tallqvist (28) who showed that the bothriocephalus latus contains oleic acid, a highly hemolytic substance, to which the anemia caused by this worm is probably due, they demonstrated in the livers of dogs poisoned with toluylendiamin the presence in large amounts of hemolytic substances of the nature of fatty acids. These were of two sorts: First, in dogs dying of very acute poisoning, a substance belonging to the fatty acids, but not oleic acid, and not associated with fatty metamorphosis in the liver, and the occurrence of which was not influenced by previous splenectomy; and second, in the more chronic cases, hemolytic higher and lower fatty acids, including oleic acid, associated with marked fatty changes in the liver. In these latter dogs, if a splenectomy was done previous to the poisoning, the amount of hemolysis shown by the liver extract was reduced to one-sixth of that of the controls, and very little fatty change was encountered in the liver. The authors also showed that proteins inhibit to a marked degree the hemolytic action of the unsaturated fatty acids.

The above results are of particular interest in view of the fact that touylenediamin poisoning leads to a condition strongly resembling hemolytic jaundice in man, with jaundice, anemia, enlargement of the spleen, and as Widal (95) has shown, increased fragility and numerous reticulated red cells.

Eppinger (27), King (47) and Medak (58) have worked along these lines in human pathology, and have reported in two cases of hemolytic jaundice a very high iodine number in the blood, indicating the presence of unsaturated fatty acids in excess. After splenectomy these patients showed a reduction of the iodine number to normal, along with other indications that the excessive hemolysis had ceased. These authors also found after splenectomy in normal dogs a decrease in the iodine number and an increase of the total fats of the blood and usually of the cholesterol.

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Dubin and Pearce (25), however, were unable to confirm these findings in so far as they relate to dogs, and Csonka (22) has criticized the technic employed in determining the iodine number, and also the method of calculation. The results of Eppinger and his school are, therefore, in need of confirmation.

The part that cholesterol plays in hemolysis within the body remains obscure. While there is no doubt that free cholesterol inhibits hemolysis in the test-tube by saponin and many other hemolytic agents, the figures obtained from chemical analysis of the blood in our disease are conflicting, and even should they be consistently low, they would not indicate whether the lower protecting power of the serum against hemolysis were primary or secondary. Further study in this direction is needed.

The presence of hemolysins in the pathological spleen has not been demonstrated as yet. In four cases of splenectomy for hemolytic jaundice, those of Vaquez and Giroux (88) Antonelli (1), and two of Kahn (45) they have been looked for in vain.

However, the influence of the spleen on hemolysis in this disease is evidently very important, for after splenectomy a virtual cure is attained, with rapid disappearance of the jaundice, and return of the blood to normal so far as red count and morphology are concerned. The fact, on the other hand, that the diminished resistance almost always persists, is against the view that the primary fault lies in the spleen.

It is possible to explain the benefit derived from splenectomy without the hypothesis of abnormal formation of hemolysins in this organ. The extensive researches of Pearce and his associates (70) have shown that splenectomy in normal dogs results in a marked reduction in the hemolytic processes, so that jaundice is much more difficult to produce with hemolytic agents than in the unoperated animal. This is partly due to the fact that normally by far the greater part of hemolysis takes place in the spleen; after splenectomy the other portions of the hemolytic system, the lymph nodes, the stellate or Kupffer cells of the liver, and the bone marrow, are unable to compensate to any marked degree for the loss of the spleen. Partly it is due to a mechanical factor, as indicated in the work of Krumbhaar, Musser and Peet (49); the hemoglobin reaches the liver after splenec-

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tomy in a more dilute form, because it comes by way of the general circulation instead of through the splenic vein. The liver is, therefore, able to handle the hemoglobin and to excrete it as bile pigment without the production of jaundice. A third factor in the difficulty of causing jaundice in the splenectomized is the increased resistance of the red cells which is uniformly present after removal of the spleen in the normal animal; apparently this does not hold good for hemolytic jaundice in man.

To sum up, our present knowledge indicates that the diminished resistance of the red cells is the leading factor in the causation of hemolytic jaundice in so far as the congenital type is concerned. It is possible that the same explanation applies to the acquired type also. Cases with normal resistance to hypotonic salt solutions might be accounted for by the assumption of abnormal fragility of a different sort, as indicated by the work of Hijmans van den Bergh (41), who demonstrated in his case increased fragility on exposure of the red cells to carbon dioxide. The spleen is a necessary link in the chain for the production of the other signs of the disease, and it is possible that its function is perverted, but that has not been proven as yet.

The pathology, diagnosis and treatment of the two types will be considered together.

Clinical picture

The jaundice. This is usually the first symptom noted, and may be present from birth, or first attract attention in childhood or early youth; exceptionally it does not occur until the age of 25, as in the case of Benjamin and Sluka (6). In well marked instances the sclerae are of a lemon-yellow color, and the skin of the body is distinctly yellow, while the face may be of a peculiar buff color which is quite characteristic. The greenish tint seen in long-standing complete obstruction of the bile ducts is never present. The jaundice may be so slight as to be apparent only on careful scrutiny. It varies in intensity from time to time, often being increased by fatigue, emotion, exposure to cold, during pregnancy, and particularly at the time of crises.

Exceptionally jaundice may be lacking, as in the family reported by Ward (89), in which the mother and maternal uncle showed mas-

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sive splenomegaly and anemia, but no jaundice, while the child showed jaundice but no enlargement of the spleen. Götzky and Isaac (34) encountered a family in which the grandmother and father were jaundiced, while the three children were anemic with enlarged spleen and increased fragility, but no icterus. Occasionally, as in the family described by Poynton (74) the jaundice is recurrent, and between attacks there are anemia and splenic tumor without icterus.

The spleen. The presence of splenic tumor constitutes one of the most striking features of the disease. Its size corresponds roughly to the severity and duration of the condition; in well marked instances it reaches to the umbilicus or even to the lowest part of the abdomen. During the crises the spleen enlarges rapidly, and there is apt to be pain in the left hypochondrium. The splenic tumor is usually discovered after the jaundice, though in the case of Schlecht (81) it was noted two and one-half years before jaundice appeared, the child being under medical observation all this time.

In a few instances, otherwise typical, enlargement of the spleen has been lacking. It was so in two brothers and a sister reported by Pick (71), and in Pollak's (72) family, in which the mother, jaundiced since birth, showed no splenic tumor, although both of her daughters had large spleens.

The blood. A moderate anemia with counts varying from 3,000,000 to 4,500,000 is the rule, but in severe crises there may be a great destruction of red cells, as in Thursfield's case (84), with 1,000,000. Guinon, Rist and Simon (37) on the other hand have reported a case, the classification of which is doubtful, in which there were jaundice and splenomegaly, but the resistance was increased and there was a transitory polyglobulia of 7,600,000.

The hemoglobin is usually proportionately reduced, so that the color index is about one. In this respect the picture resembles pernicious anemia, but it has been suggested that the high hemoglobin reading is apparent rather than real, being due to the dark color of the serum. The average size of the red cells is usually decreased; there are considerable anisocytosis and polychromia, but poikolocytosis and stippling are unusual. Normoblasts are often present in small numbers, while megaloblasts are rarely met with.

The chief interest, however, lies in the decreased resistance of the red cells to various hemolyzing agents, but especially to hypotonic

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salt solutions. This feature has been found in almost all of the reported cases, but like the other cardinal signs of this disease, it is occasionally lacking, as in the cases of Claus and Kalberlah (21), Lommel, (52) and Cade (12) while in that of Widal and Ravaut (101), the resistance was actually increased. It has been noted that the resistance may be normal at one time and decreased at another, especially during acute infections (Renaux, 75). In this connection the importance of technic should be emphasized, for if the sodium chloride is not thoroughly desiccated, too high figures will be obtained.

In most cases both the minimum and the maximum resistance are decreased, hemolysis often beginning at 0.60 per cent and being complete at 0.40 per cent, the normal figures being 0.44 to 0.48 per cent for the former, and 0.30 per cent for the latter. Sometimes only the minimum resistance is affected. Usually the results are the same with whole blood and with washed corpuscles, though some observers have found lower figures with the latter. For the technic the reader is referred to Pearce (70), page 273, and to Kolmer (48).

The resistance has also been found to be decreased to other hemolytic agents, such as anti-human hemolytic serum, cobra venom, and sometimes to saponin. Bittorf (9) showed that the resistance to acids was decreased; Grote (35) confirmed this and found the same to obtain for alkalies. Widal and others have noted that the red cells were hemolyzed by contact with normal sera, which did not hemolyze red cells derived from other persons.

Reticulation of the red cells is present to a degree met with in no other disease. This phenomenon consists in a net-work within the red cell, brought out by the so-called "vital" methods of staining, and especially well by brilliant cresyl-blue. This feature of hemolytic jaundice was first noted by Chauffard (15), who called it granular degeneration. This name should be dropped, as leading to confusion with the granular degeneration of Grawitz, or stippling, with which it has nothing to do. These reticulated or "skeined" cells occur in normal blood in small numbers, from 0.5 to 1 per cent, and in other forms of anemia up to about three per cent, while in hemolytic jaundice they make up from 10 to 20 per cent of the whole, and in the acquired type even up to 50 per cent. They are usually regarded as a sign of regeneration of the blood, as young cells that

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have reached the circulation in an immature state. It has been suggested that they are less resistant than normal cells, but this has been found not to be the case.

The white cells show no constant variations, being usually normal in number, sometimes increased, and sometimes diminished. Some observers have noted a polynuclear leucocytosis at the time of crises, in contrast to the increased leucopenia which recurs at such times in pernicious anemia, but this is not a constant finding. The differential count is about normal, with a tendency toward increase of the polynuclears. Exceptionally a few myelocytes are seen. Lommel (52) reported a very unusual case in which myeloblasts were found during pregnancy in large numbers (65 per cent), but disappeared after the induction of abortion.

The serum is almost always highly colored, owing to the presence of bilirubin. Urobilin has usually been reported absent, but according to Guillain and Troisier (36) may be found if tested for by the delicate method of Grigaut. The freezing point has been found to be markedly lowered, which indicates an increased molecular concentration of the blood. Troisier (86) explains this as a result of diffusion of the salts of the red corpuscles into the plasma.

The presence of signs pointing to increased hemolysis naturally led to a search for hemolysins in the blood, but these have been found to be almost invariably absent in the congenital type. This subject will be dealt with more fully later, under the acquired type.

Hemagglutinins likewise are very rarely encountered.

The urine. The urine is high colored, owing to an increase of urochrome, the normal urinary pigment. Bile pigment is almost invariably absent, being noted only as a transitory phenomenon in some cases at the time of crises of deglobulization. Bile salts are also absent. Urobilin and urobilinogen on the other hand are very constantly present, being absent only in cases of slight intensity. Other pigments derived from hemoglobin, such as hematoporphyrin, are absent. Albumin and sugar are not found in uncomplicated cases.

The stools: The feces are never clay-colored, but as a rule are highly colored, and show quantitatively a marked increase of urobilin. For example, Eppinger (27) found in one case a total daily excretion of 3 grams, the normal being given as 0.15 gram. This he calculates

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amounts to the destruction (and renovation) of the entire blood in the space of two days!

Metabolism. Complete studies have been made by McKelvy and Rosenbloom (54) by Goldschmidt, Pepper and Pearce (33), and by Denis (24). The fat metabolism was normal, both as regards absorption and fat-splitting. The elimination of iron was markedly increased; this is to be attributed, as is the increased urobilin excretion, to the excessive destruction of red cells. With regard to nitrogen, McKelvy and Rosenbloom found a negative balance, due, they believed, to a toxic destruction of protein, while Goldschmidt and Denis obtained positive balances.

The excretion of endogenous uric acid was found much increased by Tileston and Griffin (85), and high values were reported also by the above-mentioned writers and by Kahn (46).

McKelvy and Rosenbloom (55), in a second paper, reported a considerable loss of cholesterin in the feces, the output exceeding the intake by 7 grams in a five-day period.

The cholesterol of the blood is of interest, owing to the relation of this substance to hemolysis. According to Windaus (104), the inhibitory effect on hemolysis is exerted only by free cholesterol, not by the esters. The older publications are not of great value, owing to the lack of accurate methods. Chauffard, La Roche, and Grigaut (16) reported normal figures, as contrasted with an increase in obstructive jaundice. Studies by the more exact method of Windaus (105) and of Bloor (10) by which both free cholesterol and esters are determined, have been made in a few instances. Thus Medak (58) in one case found a low value for free cholesterol, which increased after splenectomy, mainly at the expense of the esters. King (47), however, reported a normal amount in his second case (his first case appears to have been the same patient as Medak's). In two unpublished cases studied by the writer no important variations from the normal were found.

Complications. The complication with cholelithiasis is so frequent that it might almost be considered a part of the disease. In no other condition do gall stones occur with such frequency, being present in 58 per cent of the cases operated on by W. J. Mayo (57). It is therefore natural to attribute the attacks of pain in the right

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hypochondrium, which are of frequent occurrence, to this cause. Occasionally, however, attacks of hepatic pain occur in connection with crises, and may be due simply to the overloading of the liver with the products of blood destruction.

Gout has been reported by Murchison (65), in two of the families of Tileston and Griffin (85), and in a few other cases. While it may be only a coincidence, it is also possible that the long-continued increased uric acid production might be a factor predisposing to gout. The latter differs from hemolytic jaundice in that the elimination of uric acid is diminished instead of increased.

II. THE ACQUIRED TYPE

Classification

Acquired hemolytic jaundice is divided by the French writers into two groups: first, the cryptogenetic and second, the secondary. To these a third, the hemolysinic icterus of Chauffard and Vincent (19), is sometimes added.

Etiology

The cryptogenetic group, as the name implies, is of unknown causation. The secondary variety occurs in the course of a number of diseases, chiefly infections.

Syphilis. Cases of florid lues in the secondary stage, associated with the syndrome of hemolytic jaundice have been reported by Gaucher and Giroux (30), de Beurmann Bith and Cain (7), and by Nicolas (66). The resistance was decreased in all. The striking feature is that all were cured of their hemolytic jaundice by anti-syphilitic treatment. In the case of Sablé and Darrel (78) hereditary syphilis with active bone lesions was the cause of similar symptoms, which promptly disappeared under treatment with arsphenamin. These facts contrast strongly with the negative results obtained by anti-syphilitic treatment in cases of the congenital type in which syphilis is present.

Malaria. Sacquépée (79) and others have described cases of hemolytic jaundice appearing at the time of the acute attack in malaria, and cured by quinine; the type of parasite present was not

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specified. Such cases present analogies with malarial hemoglobinuria or black-water fever.

Tuberculosis. Landouzy (50) has reported a case occuring in the "third stage" of this disease.

Other infections. The syndrome of hemolytic jaundice has been observed by Sacquépée (80) in connection with streptococcus septicemia, disappearing during convalescence. Lewin (51) found it dating from attacks of paratyphoid fever and dysentery, but in his cases the condition did not disappear with recovery from the acute infection, but became chronic. Widal, Lemierre and others (100) have described a remarkable case of septicemia due to the gas bacillus (B. aërogenes capsulatus) with hemoglobinemia and hemoglobinuria. In this case the hemolysis could be demonstrated as directly due to the action of a hemolysin secreted by the bacteria, for cultures hemolyzed blood very rapidly *in vitro*, a very exceptional phenomenon for this bacillus.

A case in which a toxic origin seems probable is that of Widal, Abrami and Brulé (98), in which the disease appeared following proctitis and ischio-rectal abscess, and got worse with the development of a stricture of the rectum; the hemolytic syndrome disappeared within a few days after the relief of the stricture by making an artificial anus. The patient remained well so long as the artificial anus functioned, but would have minor hemolytic attacks as soon as it became plugged.

Pregnancy. Roque, Chalier and Cordier (76) report a case associated with the toxemia of pregnancy. The usual signs of hemolytic jaundice were present, including diminished resistance and autoagglutination, and in addition there were multiple hemorrhages into the skin and mucous membranes. The patient was eight and one-half months pregnant and showed, as evidence of toxemia of pregnancy, general edema, amaurosis, neuroretinitis and albuminuria. Recovery ensued after the birth of a dead child.

Cirrhosis of the liver. The association with cirrhosis has been noted by Mouisset, Chalier and Nové-Josserand, (64), Chevallier and Tomkine (20) Eppinger (27) and a few others. Hemolytic jaundice occurs in both the periportal and the biliary types; the liver is almost always enlarged, and the spleen more so than is usual in ordinary cirrhosis.

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It is to be regarded as a complication of the cirrhosis and is frequently a terminal event, being in that case usually associated with infectious processes and the hemorrhagic diethesis.

A remarkable case was reported by Mosse (62), in which there was marked polyglobulia with cyanosis, splenomegaly and acholuric jaundice. The resistance was not tested. The autopsy disclosed cirrhosis of the liver.

Carcinoma. Widal and Joltrain (99) observed hemolytic jaundice in a case of carcinoma of the bladder with abundant hematuria.

Leukemia. In Gaisböck's (29) case of acute lymphatic leukemia the hemolytic syndrome, with marked diminution in resistance, was a striking feature.

Pathogenesis

In the case of the secondary form, the pathogenesis is probably different from that of the congenital type. When it occurs in connection with acute infections, the condition may be due to the action of bacterial hemolysins, and in the other instances a toxic origin seems probable.

The pathogenesis of the idiopathic variety, however, is probably similar to that of the congenital form. There is one feature that differs and that required detailed discussion, namely the presence of hemolysins in the serum. This has been noted, almost exclusively in the acquired form, by a number of observers, chiefly French. They have been chiefly isolysins, i.e., the serum hemolyzes the red cells of other persons, but not those of the patient. This is an interesting observation, but hardly explains the occurrence of hemolysis in the patient. The value of this work is considerably impaired by the fact that isolysins have been found in normal persons, Moss (61) reporting them in no less than 23 per cent. Troisier (36), however, with the technic employed, found them in only 4 per cent of 125 cases of diseases other than hemolytic jaundice.

Chauffard and Vincent (19) have set up a separate type, the so-called hemolysinic icterus, in which isolysins are present in the serum, and the resistance of the red cells is normal: a fair number of cases coming within this category has been reported. On account however of the fact that intermediate forms are met with, showing both isoly-

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sins and diminished resistance (Chauffard, Troisier and Girard, (18)), and because of the occurrence of isolysins in health, it seems best not to separate these cases.

The presence of autohemolysins on the other hand is always pathological. They have been reported in hemolytic icterus by three observers only. In the case of Chauffard and Vincent (19) in which there were hemaglobinuria and hemoglobinemia, there was slight additional hemolysis on mixing the patients serum with his own corpuscles. In view of the fact that clear serum could not be obtained for the test, there is a possibility of error.

Roth (77) reported an interesting phenomenon in a case of pernicious anemia, in which autolysins were apparently present. It was found however that the patient's red cells were hemolyzed by the sera of fifty other patients, some of which sera were hemolytic only for the red cells of the patient. He concludes that the hemolysis was due not to the presence of autolysin, but to injury to the red corpuscles, so that hemolysis occurred with the isolysins which are probably present to a greater or less degree in all sera. He points out that these tests were not made in the case of Chauffard and Vincent.

Beckmann (5), however, reported two cases (one congenital and one acquired) in which the objection of Roth was met. The hemolysis however, was but slight, so that there is a possibility of an error in technic.

Lüdke (53) has recently published some interesting observations, which if confirmed, would go far to establish the rôle of hemolysins in hemolytic jaundice. Out of four cases (two of each variety) he found autolysins present in two (one congenital, one acquired), but only during crises. Both of these cases showed slight hemaglobinuria during crises. All four showed the presence of isolysins. The test was made by mixing the patient's clear serum with the patient's washed corpuscles and adding complement (amount and kind not stated). The fact that autolysins were found during crises, but were regularly absent during the intervals, would seem to point to some causal relationship between the two.

Lüdke was apparently able to obtain experimental confirmation of his findings. He made dogs anemic by bleeding and then injecting red corpuscles from the same dog. After a single injection both

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auto and isolysins appeared in nine of eleven experiments. The splenic extracts of such dogs showed a strong hemolytic action on their own corpuscles. The splenic extract from dogs showing the presence of hemolysins, when injected intravenously into healthy dogs, caused a marked anemia with diminished resistance, while the extract of spleens from healthy dogs had no such effect. He concludes from these experiments that hemolysins may be elaborated in the spleen.

It is impossible to form a judgment of Lüdke's work without further details, which he promises to supply in a later publication. It should be noted however, that his cases were peculiar in that the Donath-Landsteiner test was positive in both, while other observers have found this test constantly negative. The demonstration of autolysins is difficult, and a standard technic has not yet been developed.

Hemagglutinins. Isoagglutinins have been shown in some cases of both types. Since, however, no attention has been paid to the presence of normal agglutinins, which Moss (61) has shown to be present in 89 per cent of healthy individuals, this work is without value. It is much to be desired that in future the agglutination-group to which the patient belongs should be determined, according to the method of Moss.

The presence of *autoagglutinins*, however, is always pathological, and is rarely met with outside of hemolytic jaundice. It has considerable theoretical as well as practical importance, since agglutination is considered by many to be a preliminary step in the process of hemolysis.

Clinical picture

The acquired type is much less frequent than the congenital, and as described by Widal (96) differs from it in several important respects.

The clinical course is more severe, ending not uncommonly in death. The anemia is more marked, the average red count according to Krumbhaar (70, page 258) being 2,000,000, against 3,300,000 for the congenital form. Counts of 1,000,000 or below are no rareties. The crises of deglobulization are more marked, and give to the disease a very chequered picture. The regeneration is at times extraordinarily rapid, as in Pollitzer's case (73), where the count rose in thirty days from 640,000 to 4,000,000. The jaundice is often less marked than in the congenital type and may be lacking.

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The resistance of the red cells is less constantly diminished, and to a lesser degree. Widal states that in this type the resistance is normal with whole blood, and diminished with washed corpuscles, but further experience has shown that this does not always obtain. Hijmans van den Bergh (41) has described an interesting case in which the resistance was normal to salt solution, but hemolysis occurred if a mixture of the patient's corpuscles and normal serum was placed in an atmosphere of carbon dioxide. The same occurred with a mixture of the patient's corpuscles and his own serum, but never in the case of normal corpuscles. He concludes that a special form of fragility was present.

Widal, Abrami and Brulé (96) have described the presence of a phenomenon, auto-agglutination of the red cells, which is almost constantly absent in the congenital type. Lüdke (53) alone has reported its occurrence in the latter. It is tested for by mixing in a watch glass one drop of the patient's corpuscles with ten drops of his own serum, and letting the mixture stand fifteen minutes at room temperature. The red cells become agglutinated into a dense pedicle which cannot be broken up by shaking. The results may be confirmed by microscopical examination. They state that auto-agglutination was present in all their acquired cases, but never in the congenital type, or in other diseases. Other authors, however, have reported less constant results, e.g., Biffis (8) found the test positive in only one of five cases.

There are in the literature a number of border-line cases between acquired hemolytic jaundice and pernicious anemia, such as those of Widal and Weissenbach (102) Weber (90) and case II of Biffis. Here with diminished fragility of the red cells and jaundice, some or all of the signs of pernicious anemia were present, and it is a question whether they should be classified as pernicious anemia with jaundice, or as a pernicious type of hemolytic jaundice. It should be noted that in pernicious anemia the resistance is almost always normal or increased. The writer has recently encountered a similar case (unpublished) in which, with increased fragility there was a rapidly progressive fatal anemia, without jaundice. The color index was low and the average diameter of the red cells not increased, normoblasts exceeded megaloblasts in number, but the autopsy disclosed a

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megaloblastic bone marrow and blood-forming foci in the liver and spleen.

Another variation from the usual type has been reported quite often, in which hemaglobinuria is a prominent feature. This may occur over long periods of time, as in case V of Biffis, or in a fulminating manner, as in that of Chauffard and Vincent (19). The Donath-Landsteiner test was negative in all. Hemoglobin was usually detected in the serum also.

An acute case of acquired hemolytic jaundice has been described by Gaisböck (29). A man twenty-two years old was seized acutely with high fever and rapidly progressive anemia, with death at the end of six weeks, after a single remission. There was constant though slight icterus; the spleen was not enlarged, except slightly during the remission. The blood showed the following signs: The red count sank to 500,000; the color index varied between 0.6 and 1.3; there was microcytosis with numerous normoblasts; leucopenia was present. The minimum resistance was much decreased while the maximum was increased. The autopsy showed a normoblastic bonemarrow, and blood-forming foci in the liver and spleen with increased pigment in the latter. Such a case may be considered as simply a more malignant form of the disease, in which death has occurred early during a crisis of deglobulization.

The question of the unity of the two types (congenital and acquired) may be considered at this point. In favor of the view which regards the two as separate entities may be advanced (*a*) the different clinical picture (*b*) the different age of onset (*c*) the lack of familial or hereditary influences, (*d*) the different etiology. As regards the first point, it should be noted that a number of congenital cases have been reported that have resembled clinically the acquired type, with grave crises and very low blood counts, while on the other hand some acquired cases, like these of Biffis (8) have shown an even course without periodic attacks, thus resembling the congenital type. The more marked fragility in the congenital type is by no means a constant difference, and even the presence of autoagglutination has been noted, though rarely, in the congenital type, as by Lüdke (53).

The resemblance of the clinical picture in the two types may be so strong that cases reported at first as acquired have been shown later,

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by the discovery of cases among the relatives, to belong to the congenital group, as in Hayem's case (40). In one of Giffin's cases (31) the finding of increased fragility in the mother, though she was free from symptoms, was the only sign leading to the correct interpretation.

The age at onset is an unreliable criterion, it being by no means uncommon to have the congenital type begin in the second decade or even somewhat later. Cases beginning after thirty, however, and these form a minority of the cases reported as acquired, apparently never show any evidence of a hereditary factor.

The third point, the lack of hereditary influences, is not of much value as a distinguishing sign. For many of the hereditary diseases, such as progressive muscular dystrophy, occur at times in only one member of a family. The fact, however, that in cases of the acquired type recovery may occur constitutes an important difference.

The most valid reason, however, for separating the two types appears to rest in the etiology. For while the cause of the congenital type remains obscure, in many of the acquired cases the treatment of some associated condition, such as lues, malaria, a stricture of the intestine, has resulted in a cure of the jaundice. This is never the case in the congenital type, even in those rare cases accompanied by hereditary syphilis.

To sum up, it is best for the present to distinguish a congenital and an acquired type. But it will be safer to consider all cases as congenital unless it can be shown that they belong to the secondary group, with undoubted relation to some infection, intoxication, or malignant disease, or unless they begin late in life, after the third decade.

PATHOLOGY OF HEMOLYTIC JAUNDICE

Our knowledge of the pathology has been derived partly from autopsy reports, partly from the examination of excised spleens. Since no differences have been found between the congenital and the acquired types, the two may be considered together.

The spleen. The gross appearances are as follows: The organ is greatly enlarged, the average weight of 12 excised spleens being 1070 grams according to Giffin, (31), and of nine spleens at autopsy 716

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grams. The capsule is often thickened and there may be adhesions to the diaphragm, both the result of old perisplenitis. The trabeculae are not thickened, the follicles appear few and small. The striking thing is the marked engorgement with blood, Guizzetti (38) remarking that the organ became reduced to one third its former size after the blood was squeezed out. Infarction has been noted in a few cases, in the absence of heart disease.

On microscopic examination the most striking thing is the marked congestion. This may be general, but often it is confined to the pulp (or "cords of Billroth"), the sinuses being empty. This peculiar distribution of the congestion was first noted by Vaquez and Giroux (88). It is unusual in other conditions; in chronic passive hyperemia for example the sinuses are engorged.

The trabeculae and reticulum show no marked degree of thickening. This constitutes an important point of distinction from Banti's disease.

The follicles appear fewer because they are widely separated owing to the congestion. They are usually normal except for the condition of the follicular arterioles, which often show a hyaline thickening, as described by Guizzetti (38), Sisto (82) and others. This change may be found also in the arterioles of the pulp, but to a lesser degree. A moderate degree of fibrosis of the follicles is sometimes encountered.

Pigment is present in the organ in varying amounts, being often very abundant, at other times scanty, or even absent, as in the case of Goldschmidt, Pepper and Pearce (33). It is chiefly within endothelial cells in the sinuses, and usually gives the iron reaction. The amount of pigment does not depend entirely on the duration of the disease, for Elliott and Kanavel (26) found very little in a man of fifty-seven years, jaundiced since birth. Phagocytosis of red cells is sometimes observed. The endothelial cells lining the sinuses may be changed from the normal flat type to an oval shape, as noted by Guizzetti and Sisto.

Liver. The size is about normal. There are no signs of cirrhosis, except in the rare cases of acquired hemolytic jaundice secondary to cirrhosis. The bile ducts are always normal, except where changes due to gall stones have occurred, as in Sisto's second case (82) with marked cholangitis and calculi in the common duct, and in the second

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case of Tileston and Giffin (85). There is no deposit of bile pigment in the liver cells. Pigmentation to a greater or less degree is the rule, being absent only in the case of Marchiafava and Nazzari (56). It may be so abundant as to compare with that of hemachromotosis; as in an unpublished case recently seen by the writer. The pigment occurs in the form of coarse brownish granules, which usually give the iron reaction. It is situated mostly in the hepatic cells, especially at the periphery of the lobules, and in the stellate or "Kupffer" cells, though some may occur in the periportal spaces. Otherwise there are no changes, except those due to intercurrent diseases. Gall stones are present in a little over 50 per cent of the cases.

Bone marrow. The bone marrow of the long bones has been found red and in a very active state, with numerous normoblasts and myelocytes, in all the cases, with the exception of case II of Sisto, in which the anemia was not marked. Pigmentation is not noted in the records.

The lymph nodes. Pigmentation has been found in a few instances; in the writer's unpublished case it was extreme, the pigment being within endothelial cells in the sinuses and giving the iron reaction. Three cases have shown the change to hemolymph nodes, with congestion, phagocytosis of red cells and pigmentation.

Kidneys. There was a very marked siderosis in the case of Minkowski (60), who isolated ½ gram of iron from one kidney; also in the case of Marchiafava and Nazzari (56), and to a lesser degree in that of Oettinger (67). The pigment is chiefly deposited in the convoluted tubules. In Marchiafava's case the pigmentation was exclusively confined to the kidneys, and the urine showed casts containing hemaglobin. This variation in the place of deposition of the pigment is interesting, suggesting that in such cases the hemaglobin is set free in the general circulation and reaches the kidneys, while as a rule the hemolysis takes place in the spleen and the pigment is deposited here, or is transported to the liver.

To sum up, the spleen shows marked congestion, often of a peculiar sort, involving the pulp but not the sinuses. The reticuloendothelial apparatus, as Aschoff calls it, namely the endothelial cells of the spleen, liver, bone marrow and lymph nodes, shows signs

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of hemolytic activity, such as phagocytosis of red cells and pigment deposit. The bone marrow shows the usual change from fatty to red marrow, as met with in most severe anemias.

DIFFERENTIAL DIAGNOSIS

Since most of the cases belong to the congenital type, a careful history, with special inquiry into the occurrence of jaundice among the relatives is of the greatest importance. The history of crises with pain and anemia is very suggestive. Any case of chronic non-obstructive jaundice, with or without enlargement of the spleen, should have the resistance of the red cells tested, and if this is lowered, the diagnosis of hemolytic jaundice is practically certain. If the resistance is normal, this does not exclude the diagnosis, provided the picture is otherwise typical. The resistance should also be tested where there is chronic anemia with splenomegaly, because hemolytic anemia without jaundice sometimes occurs. The presence of a considerable number of reticulated red cells, e.g., over 4 per cent, is valuable confirmatory evidence. The other important signs are anemia, increased urobilin excretion, the absence of bile pigment in the urine, highly colored stools and splenomegaly. Occasionally, however, any one of the above signs may be absent, and the diagnosis must rest upon the clinical picture as a whole.

In general, the diagnosis is to be made from other diseases accompanied by jaundice, diseases with splenomegaly and diseases with anemia.

1. Diseases with jaundice

Obstructive jaundice. This is excluded by the increased urobilin content and absence of decoloration of the feces, by the absence of bile pigment and bile salts from the urine, and by the absence of fatty stools. The resistance of the red cells is increased rather than diminished in obstructive jaundice.

Cholelithiasis. This is the most frequent source of error in diagnosis, owing to the fact that no less than sixty per cent of the cases of hemolytic jaundice are complicated by gall-stones. Many patients have undergone operation on the gall bladder, under the mistaken belief that the jaundice was due to calculi. It should be

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borne in mind that in disease of the gall bladder, jaundice, if present, is of the obstructive variety, and that splenic tumor is absent unless cholangitis complicates the picture, and even then is of only moderate proportions.

Acute infectious diseases with jaundice. In yellow fever and spirochetal jaundice, icterus constitutes the most striking feature. In pneumonia and streptococcal septicemia, jaundice is not infrequent. In all of these diseases it is probably hemolytic in origin. Since in such cases it is purely symptomatic, it does not require further discussion here.

Familial icterus of the new-born. This is a very rare disease, in which several children of a family are seized with deep jaundice shortly after birth, and usually die within a few days with hemorrhages and cerebral symptoms. The etiology is obscure. In the exceptional cases of recovery the jaundice disappears, so that confusion with hemolytic jaundice should not arise. It is not an hereditary disease.

2. Diseases with splenomegaly

Only those diseases associated with chronic enlargement come into question.

Banti's disease. This name is employed instead of splenic anemia as being more precise. Many cases of hemolytic jaundice have been mistaken for Banti's disease, for the two have several points in common. Banti's disease in the early stage is excluded by the presence of jaundice and of lessened resistance of the red cells, and in the later stage by the absence of indications of cirrhosis of the liver. Reticulated red cells are not abundant in Banti's disease. The occurrence of other cases in the family clinches the diagnosis of hemolytic jaundice.

Gaucher's disease, or large-celled splenomegaly. This rare disease tends to occur in several members of a family, usually the females, but is never hereditary. There is a yellowish discoloration of the skin, but true jaundice is lacking, and so far as known, the resistance of the red cells is normal. The spleen is enormously enlarged, and the liver considerably. A moderate anemia of the secondary type is present. Brill and Mandlebaum (11) have called attention to a yellowish wedge-shaped thickening of the conjunctivae, seen on both sides of the cornea, which they regard as diagnostic.

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Syphilis. Syphilis of the liver may be accompanied by great enlargement of the spleen, but jaundice is rare. The clinical picture may resemble that of Banti's disease so closely, that the diagnosis is made only at the autopsy-table. Occasionally, as noted above, both the acquired and the hereditary forms of lues may lead to true hemolytic jaundice of the acquired type, which is curable by anti-syphilitic treatment. Or again, syphilis, either acquired or hereditary, may occur as an accidental complication of the congenital type of jaundice. In such cases the finding of a positive Wassermann reaction may be misleading, but the results of a resistance test, of anti-syphilitic treatment, and the possible occurrence of jaundice in other members of the family will lead to a correct diagnosis.

Cirrhosis of the liver. The late stage of this disease is readily excluded by the absence of ascites, of signs of collateral circulation and of hemorrhage. The early stages of cirrhosis do not show much enlargement of the spleen, nor jaundice, except in the Hanot's type, where the liver is much enlarged, while in hemolytic jaundice the size is normal or only moderately increased. There is a rare juvenile form of cirrhosis, described by Jollye (44) and others, which may be familial and hence lead to difficulty. The growth is stunted, the liver is greatly enlarged and presents the lesions of biliary cirrhosis. The jaundice is of the obstructive type, the resistance presumably increased, and ascites occurs as a late feature; these points will suffice for diagnosis.

In cases of cirrhosis with an unusual degree of splenic enlargement, the possibility of a superadded hemolytic jaundice should be borne in mind, and the resistance of the red cells and the urobilin excretion measured.

Malaria. The spleen may be greatly enlarged in chronic malaria, but in the absence of acute attacks, there is no jaundice. As already noted, the syndrome of hemolytic jaundice has been observed occasionally in connection with acute malaria, in which case plasmodia can be found in the blood.

Tropical diseases with splenomegaly. Kala-azar has in common with hemolytic jaundice the splenomegaly and the anemia. There is no jaundice. Periods of fever alternate with periods of normal temperature. There are marked leucopenia and lymphocytosis. A

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positive diagnosis is made by finding the causative organism, Leishmania Donovani, in material obtained by puncture of the liver or spleen. There is also, according to Castellani and Chalmers (13) a form of tropical splenomegaly not due to this parasite, which resembles Banti's disease, but is distinguished from it by the occurrence of irregular attacks of fever.

Leukemia. The examination of the blood will suffice for diagnosis. Very rarely the occurrence of the hemolytic syndrome has been noted in this disease.

Hodgkin's disease. The spleen is often much enlarged, but in the ordinary form the marked enlargement of the lymph nodes and the absence of jaundice render confusion with hemolytic jaundice unlikely. Very rarely, however, in Hodgkin's disease, there is splenomegaly without involvement of the peripheral lymph nodes, the abdominal nodes alone being affected. In such a case jaundice may occur from pressure on the bile passages by an enlarged node; the obstructive character of the juandice and the absence of diminished resistance are sufficient to exclude hemolytic jaundice.

Polycythemia. In this disease the increased number of red cells is in marked contrast to the anemia of hemolytic jaundice. The spleen is usually considerably enlarged, but jaundice is rare. Confusion could occur only in the very exceptional borderline cases, or in the end stage of polycythemia, when there may be anemia, sometimes combined with a leukemic blood picture.

Diseases of infancy with splenomegaly. Difficulty need arise only in regard to sporadic cases of hemolytic jaundice, in which no other members of the family are affected. The so-called Von Jaksch disease and the enlarged spleen of rickets and tuberculosis are readily differentiated by the absence of jaundice. Hereditary syphilis, however, sometimes leads to icterus, and here it may be necessary to resort to a test of the resistance of the red cells as well as the Wassermann reaction, on account of the occasional association of the two diseases. In congenital obliteration of the bile ducts jaundice is intense and of the obstructive type, and therefore easily distinguished. In sepsis of the new born the presence of fever and the almost inevitable fatal outcome are distinguishing features; it should be remembered that septicemia may be, though, rarely, accompanied by the hemolytic syndrome.

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3. Diseases with anemia

Pernicious anemia is the only form that may give rise to diagnostic difficulties, and then only in the case of the acquired type of hemolytic jaundice. As already noted, a few cases occur in which it is a mere matter of opinion whether they should be classified as pernicious anemia with jaundice, or as a pernicious type of hemolytic jaundice. The resistance in pernicious anemia is usually increased, but occasionally it is diminished, as noted by Hill (42).

TREATMENT

Medical treatment

It goes without saying that all the usual methods of treatment for anemia have been tried, especially iron and arsenic. Though Widal speaks warmly of the long-continued administration of iron in the acquired type, it should be remembered that spontaneous remissions are frequent in this disease, and other writers have not noticed much benefit from this drug. The use of arsenic has also been without effect, except in those cases of the acquired type associated with active syphilis. In the congenital type of hemolytic jaundice, where hereditary syphilis is associated, no cure of the jaundice is to be expected from anti-syphilitic treatment, though some improvement in the general condition of the patient may result.

The fact that cholesterol in the test-tube inhibits hemolysis has lead to the administration of this substance. Parisot and Heully (69) noted a marked temporary improvement in the general condition, with some diminution in the jaundice and anemia, cessation of the painful crises, and increase of the resistance. Oulmont and Boidin (68) gave it to a patient with the acquired type showing diminished cholesterol in the blood, and noted that the cholesterol increased to a normal figure and the resistance also increased, but the jaundice remained unaffected. As was to be expected the effect was only temporary, ceasing as soon as the drug was stopped.

Treatment by means of the Röntgen rays has been practised by Barjon (3), Mosse (63) and others, with the result that the spleen has decreased somewhat in size, but the other signs of the disease have persisted. It is therefore not to be recommended.

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Surgical treatment

The importance of the spleen as a factor in hemolysis, and the marked enlargement of the organ, soon led to the attempt to cure the disease by removal of the spleen. The operation of splenectomy for hemolytic jaundice was first performed in the case of Vaquez and Giroux (88) and ended fatally. In 1911, however, Micheli (59) removed the spleen in a case of the acquired type with brilliant results, amounting apparently to a cure. Since then the operation has been performed with increasing frequency and most happy consequences. The jaundice disappears within a few days, and does not return. The red count rises to a normal figure, usually within a few weeks, and the urobilin excretion rapidly drops to normal, indicating a cessation of the excessive hemolysis. The lower resistance of the red cells, however, usually persists. Thus Dawson (23) reports abnormal fragility of the red cells in a patient, otherwise healthy, whose spleen had been removed twenty-seven years previously by Spencer Wells. In a few cases, however, as in that of Thursfield (84), the resistance has risen to normal and remained there.

The case of Whipham (92) has been cited as one of failure of splenectomy to cure. It occurred in a girl of six, with negative family history. The spleen was greatly enlarged and there was progressive anemia, with a red count under one million. The operation resulted in great improvement in the condition, with a return of the resistance to normal, and of the red cells to above normal (6,000,000). Three months later, however, the jaundice returned, and death occurred in a few days, without marked anemia. There was no autopsy. The intensity of the jaundice, which is described as a deep olive-green, and the fact that bile pigment was constantly present in the urine, renders this case very atypical, with a strong probability of organic disease of the liver. The case can be excluded on the ground that it was not one of pure hemolytic jaundice.

In the congenital type, a permanent cure may be predicted. Thus in Giffin's (31) series, reported from the Mayo clinic, all but one of ten patients reported themselves as well at periods up to five years after operation, and the remaining case was an atypical one of the acquired type, with probable biliary cirrhosis and a blood picture like that of pernicious anemia. Also in cases of the acquired

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type, unless they are secondary to grave and incurable disease (cirrhosis, carcinoma, etc.) the prospects for cure are excellent.

The immediate mortality, high in earlier cases, has been greatly reduced, so that Mayo (57) was able to report nineteen operations with but one death (5.3 per cent). This has been accomplished partly by improvement in technic, partly by the transfusion of blood before, and also afterwards if much blood has been lost.

The operation is therefore to be recommended in the congenital type if the symptoms are sufficiently severe, and in the "primary" cases of the acquired type. Where the condition is secondary to other disease, each case will have to be decided on its merits, bearing in mind that splenectomy will almost certainly decrease the hemolysis, but will not influence organic disease in other parts of the body.

The question of an operation for gall stones often arises in these patients. It is probably best to do the splenectomy first, and if the condition of the patient permits, to remove the gall stones at the same operation. This was successfully accomplished in a case recently studied by the writer. The removal of the spleen alone usually does not suffice, the attacks of biliary colic recurring after the operation.

PROGNOSIS

In the congenital type the prognosis is good as to life, there being almost no instances of death from the disease itself. But the frequent complication by gall-stones, the chronic anemia and crises of deglobulization, make the condition of many of these patients more or less miserable. Usually as old age approaches, the anemia becomes less and crises rarer, but apart from operative measures, this is the most that can be held out to the sufferer, for the condition persists throughout life. The brilliant effects of splenectomy have been considered above.

The prognosis in the acquired type is less favorable, death in many instances resulting directly from the anemia or from intercurrent infections. Recovery may occur spontaneously, but is not the rule. The course is in general more severe than in the congenital type, and the patient is usually incapacitated for work for long periods. The operation of splenectomy offers excellent chances for cure in the primary or cryptogenetic form, except in the cases bordering on pernicious anemia.

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REFERENCES

(1) Antonelli, G.: Policlinico, 1913, xx, Sez. Med., 97, 170, 193.
(2) Banti, G.: Semaine méd., 1913, xxxiii, 313.
(3) Barjon: Lyon méd. 1914, cxxii, 1029.
(4) Barlow, T., and Shaw, H. B.: Tr. Clin. Soc. London, 1902, xxxv, 155.
(5) Beckman, K.: Deutsch. Arch. f. klin. Med., 1918, cxxvi, 305.
(6) Benjamin, E., and Sluka, E.: Berl. klin. Wchnschr., 1907, xliv, 1065.
(7) de Beurmann, Bith, and Cain: Bull. et mém. Soc. méd. d. hôp. de Paris, 1910, xxx, 636.
(8) Biffis, P.: Riforma med., 1915, xxxi, 11, 42, 64, 95.
(9) Bittorf: Verhandl. d. deutsch. Kongr. f. Inn. med., 1914, xxxi, 619.
(10) Bloor, W. R., and Knudson, A.: Jour. Biol. Chem., 1916, xxvii, 107.
(11) Brill, N. E., and Mandlebaum, F. S.: Amer. Jour. Med. Sci., 1913, cxlvi, 863.
(12) Cade, A.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxvi, 421.
(13) Castellani, A. and Chalmers, A. J.: Manual of Tropical Medicine 3rd Edition, 1919, 1303.
(14) Chauffard, A.: Semaine méd. 1907, xxvii, 25.
(15) Chauffard, A.: Semaine méd. 1908, xxviii, 49.
(16) Chauffard, A., Laroche, G., and Grigaut: Compt. rend. Soc. de biol., 1911, lxx, 20.
(17) Chauffard, A.: Ann. de Méd., 1914, i, 1.
(18) Chauffard, A., Troisier, J., and Girard, L.: Bull. et mem. Soc. méd. d. Hôp. de Paris., 1912, xxxiii, 726.
(19) Chauffard, A., Vincent, C.: Semaine méd., 1909, xxix, 601.
(20) Chevallier, P., and Tomkine, J.: Folia haematol., 1915, xix, 244.
(21) Claus and Kalberlah: Berl. klin. Wchnschr., 1906, xliii, 1471.
(22) Csonka, F. S.: Jour. Biol. Chem., 1916, xxiv, 431.
(23) Dawson, B.: Proc. Roy. Soc. of Med., London, 1914, vii, part 1, clin. sect., 85.
(24) Denis, W.: Arch. Int. Med., 1917, xx, 79.
(25) Dubin, H., and Pearce, R. M.: Arch. Int. Med., 1916, xviii, 426.
(26) Elliott, C. A., and Kanavel, A. B.: Surg. Gynec. and Obst., 1915, xxi, 21.
(27) Eppinger, H.: Berl. klin. Wchnschr., 1913, l, 1509, 1572.
(28) Faust, E. S., and Tallqvist, T. W.: Arch. f. exper. Path. u. Pharmakol, 1907, lvii, 367.
(29) Gaisböck, F.: Deutsch. Arch. f. klin. Med., 1913, cx, 413.
(30) Gaucher and Giroux.: Ann. d. Mal. Vénériennes, 1910, v, 251. Bull. de l'Acad. de Méd., Paris, 1911, lxv, 446.
(31) Giffin, H. Z.: Surg., Gyn. and Obst., 1917, xxv, 152.
(32) Gilbert, A., Castaigne, and Lereboullet: Bull. et mém. Soc. méd. d. hop. de Paris, 1900, xvii, 948.
(33) Goldschmidt, S., Pepper, O. H. P., and Pearce, R. M.: Arch. Int. Med., 1915, xvi, 437.
(34) Götzsky, F., and Isaac, S.: Folia Haematol., 1913, xvii, Arch., 128.
(35) Grote, L. R.: Zeitschr. f. klin. Med., 1918, lxxxvi, 266.
(36) Guillain, G., and Troisier, J: Congrès. Franc. de Méd., 1911, xii, Rapports, 135.
(37) Guinon, L., Rist, E. and Simon, L. G.: Bull. et mém. Soc. méd. d. Hop. d. Paris, 1904, xxi, 786.

Digitized by Google

(38) GUIZZETTI, P.: Beitr. z. path. Anat. u. z. allg. Path., 1912, lii, 15.
(39) HAYEM, G., Presse Méd., 1898, i., 121.
(40) HAYEM, G., Bull. et mém. Soc. méd. d. Hôp. d. Paris, 1908, xxv, 122.
(41) HIJMANS VAN DEN BERGH, A. A.: Rev. de Méd., 1911, xxxi, 63.
(42) HILL, L. W.: Arch. Int. Med., 1915, xvi, 809.
(43) JOANNOVICS, G., AND PICK, E. P., ZEITSCHR. f. exp. Path. u. Ther., 1910, vii, 185.
(44) JOLLYE: Brit. M. J., 1892, i, 858.
(45) KAHN, F.: Verhandl. d. deutsch. Cong. f. inn. Med., 1913, xxx, 326.
(46) KAHN, F.: Verhandl. d. deutsch. Congr. f. inn. Med., 1914, xxxi, 633.
(47) KING, J. K.: Arch. Int. Med., 1914, xiv, 145.
(48) KOLMER, J. A.: Infection, Immunity and Specific Therapy, 1915, 380.
(49) KRUMBHAAR, E. B., MUSSER, J. H., JR., AND PEET, M. M.: J. Exper. M., 1916, xxiii, 97.
(50) LANDOUZY, L.: Presse méd., 1910, xviii, 760.
(51) LEWIN, C.: Med. Klin., 1920, xvi, 137.
(52) LOMMEL, F.: Deutsch. Arch. f. klin. Med., 1913, cix, 174.
(53) LÜDKE, H.: München. med. Wchnschr., 1918, lxv, 1098.
(54) MCKELVY, J. P., AND ROSENBLOOM, J.: Arch. Int. Med., 1915, xv, 227.
(55) MCKELVY, J. P., AND ROSENBLOOM, J.: Biochem. Ztschr., 1915, lxviii, 78.
(56) MARCHIAFAVA, E., AND NAZZARI, A.: Policlinico, 1911, xviii, Sez. med. 241.
(57) MAYO, W. J.: Med. Rec., New York, 1917, xcii, 705.
(58) MEDAK, E.: Biochem. Ztschr., 1914, lix, 419.
(59) MICHELI, F.: Wien. klin. Wchnschr., 1911, xxiv, 1269.
(60) MINKOWSKI, O.: Verhandl. d. deutsch. Kongr. f. inn. Med., 1900, xviii, 316.
(61) MOSS, W. L.: Bull. Johns Hopkins Hosp., 1910, xxi, 63.
(62) MOSSE, M.: Deutsch. med. Wchnschr., 1907, xxxiii, 2175. Ztschr. f. klin. Med., 1914, lxxix, 431.
(63) MOSSE, M.: Berl. klin. Wchnschr., 1912, xlix, 1795.
(64) MOUISSET, A., CHALIER, J., AND NOVÉ-JOSSERAND, L.: Lyon méd., 1910, cxiv, 141.
(65) MURCHISON, C.: Diseases of the Liver, 3rd. Edition, 1885, 481.
(66) NICOLAS, MASSIA, ET AL., Lyon méd., 1914, cxxii, 609.
(67) OETTINGER, W.: Bull. et. mém. Soc. mém. d. hôp. de Par., 1908, xxvi, 391.
(68) OULMONT AND BOIDIN: Presse med., 1912, xx, 525.
(69) PARISOT, J., AND HEULLY, L.,: Bull. et mém. Soc. méd. d. hôp. de Par., 1912, xxxiv, 527.
(70) PEARCE, R. M., KRUMBHAAR, E. B., AND FRAZIER, C. H.: The Spleen and Anemia, Philadelphia, 1918.
(71) PICK, A.: Wien. klin. Wchnschr., 1903, xvi, 493.
(72) POLLAK, R.: Wien. med. Wchnschr., 1908, lviii, 1489.
(73) POLLITZER, H., Ztschr. f. klin. Med., 1912, lxxv, 367.
(74) POYNTON, F. J.: Lancet, 1910, i, 153.
(75) RENAUX, E.: Jour. méd. d. Bruxelles, 1910, xv, 661, 677.
(76) ROQUE, G., CHALIER, J., AND CORDIER, V.: Lyon méd., 1909, cxiii, 961.
(77) ROTH, O.: Deutsch. Arch. f. klin. Med., 1913, cx, 77.
(78) SABLÉ, J., AND DARREL, L.: Bull.et mém. Soc. méd. d. hop. de Par., 1911, xxxii, 657.
(79) SACQUÉPÉE, E.: Bull. et mém. Soc. méd. d. hop. de Par., 1908, xxvi, 361.
(80) SACQUÉPÉE, E.: Bull. et. mém. Soc. méd. d. hop. de Par., 1909, xxvii, 164.
(81) SCHLECHT: München. med. Wchnschr., 1913, lx, 558.

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(82) Sisto, P.: Clinica med. Ital., 1914, liii, 497.
(83) Thayer, W. S., and Morris, R. S., Bull. Johns Hopkins Hosp., 1911, xxii, 85.
(84) Thursfield, H.: Proc. Roy. Soc. Med., 1913, vii, Clin. Sect. 84.
(85) Tileston, W., and Griffin, W. A.: Am. J. M. Sc., 1910, cxxxix, 847.
(86) Trousier, J.: Role des Hémolysines dans la genèse des Pigments Biliaires et de l' Urobiline, Thèse de Paris, 1910.
(87) Türk, W.: Deutsch. med. Wchnschr., 1914, xl, 371.
(88) Vaquez, H., and Giroux: Bull. et mém. Soc. méd. d. hôp. de Par., 1907, xxiv, 1184.
(89) Ward, G. R.: Brit. J. Child. Dis., 1914, xi, 214.
(90) Weber, F. P.: Am. J. M. Sc., 1909, cxxxviii, 24.
(91) Weber, F. P.: Brit. J. Child. Dis., 1914, xi, 345.
(92) Whipham, T. R. C.: Lancet, 1914, ii, 1194.
(93) Whipple, G. H., and Hooper, C. W.: J. Exper. M., 1913, xvii, 593, and 612.
(94) Widal, F., Abrami, P., and Brulé, M.: Presse méd., 1907, xv, 641.
(95) Widal, F., Abrami, P., and Brulé, M.: Bull. et. mém. Soc. méd. d. hop. de Par., 1907, xxiv, 1354.
(96) Widal, F., Abrami, P., and Brulé, M., Arch. d. mal. du coeur, 1908, i, 193.
(97) Widal, F., Abrami, P., and Brulé, M., Congr. Franç d. méd., 1911, xii, Rapports 232.
(98) Widal, F., Abrami, P., and Brulé, M., Bull. et mém. Soc. méd. d. hop. de Par., 1912, xxxiii, 480.
(99) Widal, F., and Joltrain: Bull. et mém. Soc. méd. d. hop. de Par., 1908, xxv, 468.
(100) Widal, F. Lemierre, A., et al.: Bull. et mém. Soc. méd. d. Hop. de Par., 1911, xxxii, 334.
(101) Widal, F., and Ravaut, P., Bull. et mém. Soc. méd. d. Hop. de Par., 1902, xix, 984.
(102) Widal, F., and Weissenbach, R. J.: Bull. et mém. Soc. méd. d. Hop. de Par., 1913, xxxvi, 250.
(103) Wilson, C.: Tr. Clin. Soc. London, 1890, xxiii, 162.
(104) Windaus, A.: Berl. Chem. Ges., 1909, xlii, 238.
(105) Windaus, A.: Ztschr. f. physiol. Chem., 1910, lxv, 110.

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A BACTERIOLOGICAL AND CLINICAL CONSIDERATION OF BACILLARY DYSENTERY IN ADULTS AND CHILDREN

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I. INTRODUCTION*

The term dysentery (Δυσεντερια) (bowel trouble) was introduced by Hippocrates (1) to denote a condition characterized by the frequent passage of stools containing blood and mucus, accompanied by straining and tenesmus. Some of the cases that were described at that time (1) were doubtless amebic in origin for the occurrence of liver complications is mentioned. The outbreak in Xerxes' army during the Grecian campaign in 480 B.C. (2), however, was very likely bacillary.

Not until the discovery of the ameba histolytica and B. dysenteriae at the end of the last century could epidemics of bacillary dysentery be accurately differentiated from those of the amebic variety. Only by noting the absence of liver complications in the older chronicles can it be assumed that bacillary dysentery was the type described, and even then one is not always justified in so doing, for other infectious processes in the intestinal tract (paratyphoid-Gaertner group) may occasionally present a clinical picture similar to bacillary dysentery. It is now well known that large single abscesses of the liver complicate only the amebic form of the disease while even multiple small pyemic abscesses are rare in bacillary dysentery. Rogers (3) states that the conditions under which dysentery occurs may be of assistance in determining the type of the disease. "Epidemic dysentery in asylums, jails or in long occupied and unsanitary military camps during war is nearly certain to be bacillary, while sporadic cases in a warm climate are more frequently amebic."

*I am indebted to Hirsch (4), Kartulis (5), Rogers (3), Gettings (6), Castellani and Chalmers (7) for many historical details.

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Dysentery among the civilian population (historical data)

Epidemics of dysentery prior to the time of Hippocrates cannot be differentiated into amebic and bacillary varieties. The disease is mentioned in Papyrus Ebers (8). Atisar is its name in the older commentaries of British India (9). Although acute and chronic types of dysentery were mentioned, hepatic complications are not recorded. Probably amebic and bacillary types were considered together for both occur in India (10, 11, 12). The etiology of the cases of dysentery described by Aretaeus (13), Celsus (14), Archigenes (15), Caius Arelianus (16) and Avicenna (17) is doubtful. The outbreaks noted in Europe throughout the middle ages (18, 19, 20, 21, 22, 23) were probably bacillary in origin for the intestines appeared to be the sole seat of the disease. Sydenham's (24) (1669) descriptions of the disease in London and Pringle's (25) reports of the outbreak of dysentery in the army in Flanders (1752) do not mention hepatic complications and are but little different from the records of the dysentery epidemics in recent years which have been proved to have been due to infection with B. dysenteriae. Symptoms, autopsies and, it might be mentioned, even medicinal treatment are practically identical. In the middle ages, epidemics of dysentery were apparently of very frequent occurrence (4).

In England (6, 26) from the beginning of the seventeenth to the middle of the nineteenth century epidemics of bacillary dysentery appeared more or less regularly at twenty-year intervals. It would seem as if the disease would attack each generation, render the survivers immune and then wait for the non-immune offspring.

It would be merely repetition to record the extensive epidemics of dysentery that have been reported. From Iceland to Africa they have been numerous. Epidemics were recorded in North America in the middle of the eighteenth century (27) probably introduced from Europe. Hirsch (4), Kartulis (5), Rogers (3), Gettings (6) and others (7) have completely covered this historical aspect. The importance and efficacy of modern sanitation in times of peace are clearly illustrated by the practical disappearance of extensive epidemics of dysentery from the civilian population. It is not to be denied that the disease is still a menace (28, 29), for it claims many victims especially among

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children and the inmates of jails and asylums. In such institutions the high incidence of bacillary dysentery is noteworthy. Baly (30) in 1847 focused attention on its prevalence in English jails and pointed out that not a single liver abscess had been found in Milbank prison among the hundreds of dysentery necropsies from 1823 to 1847 and furthermore that in his experience ipecac which physicians in India had found so efficacious was useless. MacKinnon (31) in 1848 reported a similar condition in the Indian jails. In the insane asylums of England (6, 32) and of the United States bacillary dysentery has proved to be a serious problem. These cases of so-called "asylum dysentery" have now been proved to be due to infection with B. dysenteriae (33, 34, 35, 36, 37, 38). It does not appear (39) to be a seasonal disease whereas the dysentery of barracks and camps is generally much more prevalent in summer and autumn.

Mild, sporadic cases of bacillary dysentery still occur in England (40) and in the United States more frequently than is generally recognized.

Dysentery in children (historical data)

The reduction of the incidence of dysentery in children has not been as marked as in adults (civilians). This may be due to the fact that until the present century it was not recognized that many of the bloody diarrheas of childhood were really cases of dysentery although since 1829 various surmises have been advanced in regard to its infectious or "miasmatic" nature (4). Aretaeus in the second century, Harris in London in 1650 and others (26) mentioned infantile diarrhea and Benjamin Rush (41) in 1777 emphasized the prevalence and serious consequences of bloody diarrhea in infants in the United States. The condition was probably unknown among the American Indians (42). During the nineteenth century the disease was discussed under various names. The medical literature, both American and European, is replete with descriptions of, and observations on, "cholera infantum." This term covered a multitude of sins and not the least of these was bacillary dysentery. The clinical descriptions and autopsies reported by Jackson, Warren (43), and Horner (44) of Boston and others (45, 62) in children with "cholera infantum" and "bloody diarrhea" are similar to those we have had in the past few years

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in cases from which B. dysenteriae was isolated. Ekiri (46) was the name given to epidemic infantile diarrhea in Japan and this also is now proved (47, 389) to be bacillary dysentery. At present the disease in children frequently escapes official notice by masquerading under other names of which ileocolitis and "infectious diarrhea" are the more common. Under the blanket term "summer diarrhea" many cases of infantile dysentery are hidden. Although we seldom see epidemics such as were recorded in this country in Revolutionary times, yet many sporadic cases still occur (48).

Dysentery in troops (historical data)

Practically every long campaign and extended siege since the memory of man has produced an epidemic of dysentery. The "emerods" with which the Bible states the army of the Philistines was smitten are now interpreted (350) as prolapses of the rectum occurring in epidemic dysentery. During military campaigns, Edward I and Henry V of England died of this disease. Seventy-five per cent of the latter's army succumbed to dysentery (6). The armies in the Peloponnesian war (4), the British campaigns in the 18th century (49, 50), Napoleon's campaigns, the Crimean war (51), the American Civil war (52), the Franco-Prussian war (6) and the Chino-Japanese war probably paid heavier toll to B. dysenteriae than to Mars. In 1914 Osler (53) said that while typhoid fever would be controlled, dysentery would play havoc. It did. Early in 1915 the hospital ships returned from the Dardanelles (54) laden with cases of dysentery. The Belgians and British in Flanders (55, 56, 383), the British in Salonika (57, 58), Gallipoli (54, 59), Mesopotamia (60, 61, 370), Palestine (63, 380), and Egypt (64), and the French in the Argonne (65) and the East (66) suffered also, while the American army, though later in entering the war, had numerous cases at Chateau Thierry and at the base ports (67, 68). The Germans (69, 70, 71, 72, 73, 433) and the Austrians (74, 75) suffered especially along their Eastern fronts, and even found a new type (Schmitz) (76) of dysentery bacillus among their Roumanian prisoners.

In fact, from the standpoint of the prevention of dysentery in campaigns we are nearly as badly off as Xenophon (2) was during the Greek retreat from Persia.

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II. ETIOLOGY

Progress toward the discovery of B. dysenteriae

Emanations from the soil, humidity, altitude, atmospheric changes and other conditions were formerly believed to act as causes of dysentery, and occupation, age, race and previous health as predisposing factors.

Pringle (25) in 1752 after discussing heat and humidity as the remote causes and putrefaction of the blood and scurvy as predisposing factors, concludes with the prophetic statement "But having since perused the curious dissertation of Linnaeus in favor of Kercher's suggestion of contagion by animalculae, it seems reasonable to suspend all hypothesis until that matter is further inquired into."

Lambl (81) in Prague in 1859 made the first step toward unshrouding the mystery by describing amebae in the stools of a child dying of diarrhea. Although he strongly urged the possibility that this might be the real cause of the disease, others (82) were not absolutely convinced of it. Eighteen years later Loesch (83) in Petrograd found numerous amebae both before and after death in dysentery cases. He went one step farther and produced symptoms of dysentery in dogs with this parasite. Kartulis (84) (1883) in Egypt demonstrated amebae in sections of the intestinal walls of all of the 150 dysentery necropsies he studied. This apparently settled the question until Massiocetine (85) in 1889 found amebae in patients without dysenteric symptoms. Grave doubts were then expressed in regard to the pathogenicity of amoebae.

However, after Kartulis (84) in Egypt in 1886 had demonstrated amebae in the liver abscesses of patients who had had dysentery and Osler (86) in 1890 had confirmed the finding, Councilman and Lafleur (87) (1891) settled the pathogenicity of amebae by differentiating amebae coli which occur in normal stools from amebae dysenteriae which produce dysentery. They also remarked that a diphtheritic type of dysentery, which we now know to be bacillary, could be distinguished from amebic dysentery. These researches were soon verified by Schaudinn (88) and the name ameba histolytica was applied to the pathogenic variety.

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It now appears that in rare cases, symptoms of dysentery may be due to certain other parasites such as balantidium coli (89, 90), lamblia (91), trichomonas (92, 93), ankylostoma, schistosoma, paragonimus (265), chilomastix mesnili (364) and bilharzia (94), which up to the present have received little attention.

Stool cultures (historical)

During this period of controversy over amebae, many investigators still clung to the belief that some, if not all, cases of dysentery were caused by bacteria. In 1869, ten years after Lambl's discovery, Basch (95) reported the presence of leptothrix filaments in sections of the intestines of patients dying of dysentery. From that date on, various workers described different organisms as the cause of this disease. The earlier investigators believed that many species of organisms (polymicrobic theory) could cause dysentery but Klebs (96) (1887), Chantemesse and Widal (97) (1888) Grigoriew (98) (1892), Ogate (99) (1892) and Celli (100) (1896) each advocated a single variety of bacillus as the etiological agent. Many authorities believe that Chantemesse and Widal described a bacillus similar to that finally reported by Shiga although it was claimed that their organism could produce dysentery in guinea pigs, a phenomenon that cannot be reproduced with B. dysenteriae. Maggiora (101), Arnaud (102) and numerous others (103, 104) claimed that B. coli of exalted virulence produced dysentery. B. pyocyaneus was urged as the cause of dysentery by Calmette (105) (1893) working in Cochin China and also by others (106) in America. The streptococcus was reported as the cause in 1896 by Durham, Mott (32) and others (107, 351). B. proteus has also had many supporters (62, 108). B. fecalis alkaligenes (406, 432), B. enteritidis sporogenes (169) and B. lactis aerogenes (407), are occasionally reported as causes of dysentery.

All of these investigators found these various organisms in the excreta of dysentery patients but no one advanced any real proof that there was a causal relationship between any of these bacteria and the disease dysentery. We know now that the streptococci, B. pyocyaneus, B. proteus and these other organisms, although frequently present in dysentery stools are probably without etiological significance.

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In 1898 Shiga (77) conclusively proved that a specific organism which has been named after him was present in the stools of many patients with dysentery and that agglutinins for it were present in the patient's serum. Furthermore, it was not present in normal stools. When injected into rabbits, symptoms of dysentery and toxemia resulted. It soon became apparent that this organism was the cause of the cases of dysentery that Shiga studied.

Two years later Flexner (109) found bacilli which were supposed to be identical with Shiga's organism in cases of dysentery in the Philippines. In the same year Kruse (34) found in Westphalia an organism identical with that of Shiga. In an epidemic of dysentery occurring in a German insane asylum, he also discovered a bacillus that differed in its agglutination reactions from the original Shiga organism. This he called B pseudodysenteriae. Both types were soon demonstrated (33) in cases of dysentery in the United States.

In 1902 Martini and Lentz (110) developed a method for distinguishing the Shiga bacillus from Flexner's bacillus and Kruse's pseudodysentery bacillus by means of agglutination tests and the fermentation of mannite. The former failed to ferment this carbohydrate while the two latter produced acid and no gas.

Park (111) carried out mannite fermentation tests on the organism Flexner had recovered in the Philippines and noted that it produced acid and no gas and therefore was similar to Kruse's B. pseudodysenteriae and not to the Shiga bacillus. It also fermented maltose and saccharose. This is the organism which is now known as the Flexner-Harris bacillus.

In 1902–1903 Strong (112) isolated a mannite fermenting bacillus differing in maltose fermentation from Flexner's organism that also satisfied all of Shiga's postulates for a causative organism. It was found in dysentery stools, it was agglutinated by patients' sera and furthermore when fed to a condemned prisoner it produced dysentery.

In 1903 Hiss and Russell (113) found a mannite fermenting bacillus in the stools of a child with dysentery. This organism, which was christened the Y bacillus, failed to ferment maltose and saccharose and thus differed from the the Flexner-Harris and Strong bacilli. Some authors (133) differ in their reports on the maltose and saccharose reactions of these organisms.

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The four organisms, Shiga, Flexner-Harris, Strong and Hiss-Russell-Y have been considered distinct varieties and the most common types The first does not ferment mannite; the last three do, but are separated from each other by differences in the fermentation of maltose and saccharose. The serum of rabbits immunized with the Shiga bacillus will agglutinate practically all strains of dysentery bacilli of similar cultural characteristics. Solimano (373) believes that the biochemical reactions of the Shiga bacillus are its only constant factor and that its agglutination reactions are variable. Cultures of B. dysenteriae (Shiga) it is true are encountered that are or can be rendered inagglutinable (114, 115) but the instances are rare. Ordinary laboratory cultivation usually causes these organisms to become more sensitive to agglutination (431). Serum from animals immunized with the Shiga bacillus will not usually agglutinate any of the mannite fermenting cultures to very high titres.

Monovalent sera made from the three main members of the mannite fermenting group (Flexner-Harris, Strong and Y) although usually agglutinating the homologous strain to higher titres will also often agglutinate the other members of the mannite-fermenting group to partial titre and will sometimes even agglutinate the Shiga bacillus in lower dilutions. In other words, it appears that there are two distinct groups, the non-mannite fermenting bacilli with a single variety, Shiga, and the mannite-fermenting bacilli with three subgroups, Flexner-Harris, Strong and Hiss-Russell-Y.

Etiology of "bloody diarrhea" in children

A great advance in the study of diarrhea in children was made by Duval and Bassett (215) who in 1902 showed that many cases of so-called "summer diarrhea" in infants were due to infection with B. dysenteriae. The Rockefeller Commission (138) in the following summer confirmed the discovery. Similar findings have been reported by other investigators in various parts of the United States, Europe and Japan (40, 47, 48, 124, 149, 150, 151, 152, 153, 154, 389). Tenbroek and Norbury (154) in Boston found dysentery bacilli and agglutinins in the blood of 80 per cent of their patients with bloody diarrhea. My results (48) in a series of patients with bloody stools in Baltimore and Birmingham were identical with those of Tenbroek

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and Norbury (154). A clinical analysis of all of these cases of dysenteric infection in children reported by various authors shows that it is practically only from patients who have, or have had, bloody, purulent and mucous stools that B. dysenteriae is isolated. In this country and Japan, bacillary dysentery in children is usually due to infection with B. dysenteriae Flexner. Only 12.5 per cent of my cases (48) and 10 per cent of Mita's cases (389) were of the Shiga variety.

Dysentery bacilli have occasionally been reported in the stools of apparently normal infants (153, 155, 156) and adults (47, 117) who have usually, however, been in contact with patients with dysentery and are probably carriers. They have been isolated from sources having no connection with dysentery patients (157). Many of these cultures are inagglutinable (158) and probably are not true dysentery bacilli. I was unable to find typical dysentery bacilli in the stools of 100 normal children and of 63 children with diarrhea (48) whose stools contained no blood and but little mucus.

Dysentery in children stands out sharply on clinical as well as bacteriological grounds. In fact, in the published studies (138, 154, 48) made in several of the larger cities in the United States, approximately 80 per cent of all of the cases of bloody and mucous diarrhea in children have been proved to be due to infection with B. dysenteriae.

It is thus apparent that ileocolitis and bacillary dysentery in children are one and the same disease. They should be called dysentery. There seems no justification for calling the same disease in children and adults by different names. Nevertheless, many types of diarrhea in children during the warm months, regardless of etiology, are often classed together as "summer diarrhea."

Many bacteriological studies of the stools of children with diarrhea have been made and numerous different organisms have been brought forward as the etiological agents of this condition. The old contention (159) that B. welchii (gas bacillus) was one of the causes of diarrhea in children has been discredited. Numerous investigators (48, 154, 160, 161, 162, 163) have shown that this organism is present in the stools of many normal children and has nothing to do with the etiology of diarrhea.

Several investigators have maintained that B. Morgan No. 1 was the cause of diarrhea in children (164, 165) and also in adults (354).

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Numerous investigations (48, 63, 66, 68, 154, 166, 167, 168, 430), have disclosed the fact that this organism is a motile Gram-negative bacillus characterized by the production of acid and gas in the monosaccharides only, the formation of indol and the non-liquefaction of gelatin. It produces an endotoxin fatal for rabbits but no exotoxin (430). B. Morgan probably represents a wide group of bacilli rather than a single type. It is also present in the stools of many normal children and adults. Furthermore the serum of patients with diarrhea in whose stools B. Morgan No. 1 is found, do not have agglutinins for this organism (48, 154, 166) so that it would seem highly improbable that B. Morgan No. 1 is of etiological importance in diarrhea.

The claims that B. pyocyaneus (106), streptococcus fecalis (107), B. proteus (63, 108, 170) and highly virulent colon bacilli are the cause of diarrhea in children have all been frequently refuted (48, 154, 163).

Several investigators (171, 172) have advanced the theory that the diarrheas of children are caused by the effects of a putrefactive or a fermentative flora. The idea has been recently emphasized in the United States (173). Our studies (163) have revealed the fact that the so-called putrefactive and fermentative intestinal flora that have been supposed to produce diarrhea, frequently exist in normal children without causing the slightest change in the patient's health. The putrefaction and fermentation theory of intestinal disease in children is an old one and originated with Jackson (43) of Boston in 1812. "In some cases in which symptoms of dysentery had occurred there was postmortem inflammation of the large intestine which is attributable to the putrefaction of animal food and the acetous fermentation of that which is vegetable." Proof has not yet arisen that gives this theory any more stability than it had in 1812.

The toxins of the Shiga bacillus

Shiga (77) first pointed out that the bacillus which bears his name was highly toxic for rabbits. The Shiga bacillus or its poisonous products induces two kinds of marked lesions in the rabbit (77, 78, 116, 117, 118, 119, 120, 121); one is localized in the intestine, and the other in the central nervous system. Olitsky and Kligler (119) have isolated two toxins from cultures of B. dysenteriae (Shiga) and have dem-

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onstrated that they are physically and biologically distinct. The Shiga bacillus grown in egg albumen broth yields in the first few days of the cultivation, at the beginning of the alkaline phase of its growth and before bacterial disintegration sets in, a toxic product which appears in the bacteria-free filtrate. This toxic product is precipitated with the globulin fraction of the protein, is relatively heat labile, being destroyed when heated to 75°C. for one hour, and is capable of inciting antitoxin formation. It is constant in its properties, regardless of the source of the Shiga culture, i.e., an antitoxin produced by the injection of one Shiga culture will neutralize the toxins of other Shiga cultures from widely separated sources. This toxin will produce in rabbits after a definite incubation period, typical lesions of the central nervous system (hemorrhages, necroses, and possibly a perivascular infiltration in the gray matter of the upper spinal cord and medulla) with paralysis of the limbs and urinary bladder (vide infra). It will not produce any obvious intestinal lesions. Olitsky and Kligler (119) regard it as an *exotoxin* and a *neurotoxin*.

The production of the *endotoxin* of Shiga bacilli does not differ essentially from that of other bacteria. The principle underlying all of the methods is that of autolysis or dissolution of the bacterial cell with the resultant liberation of its intracellular components. Most observations with the Shiga bacillus have been made with endotoxins produced in broth cultures by prolonged incubation (beyond fourteen days), but endotoxin may be produced more rapidly by incubating at 37°C. for forty-eight hours a saline suspension of a twenty-four-hour agar slant culture and then filtering through a Berkefeld N candle (119).

Usually small amounts of exotoxin are found in preparations of endotoxin and vice versa but they may be separated by heat for the exotoxin is destroyed when heated to 75°C. for one hour while the endotoxin will withstand this temperature although it is destroyed when heated to 85–90°C. for one hour. These two toxins may also be separated by neutralization, i.e., by adding anti-exotoxin, all of the exotoxin present is combined and neutralized and only the endotoxin remains free and active. Anti-exotoxin will not neutralize endotoxin. Endotoxin, however, is neutralized by an antibacterial serum prepared by actively immunizing horses with Shiga bacilli.

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The endotoxin exerts a typical action on the intestinal tract of rabbits producing edema, hemorrhage, necroses, and ulcerations especially in the cecum and large intestine (vide infra). The Shiga endotoxin is probably of intracellular origin, and has the properties of the endotoxins as a class (119). Neitz (122) extracted a nucleo-protein from Shiga bacilli that was toxic for animals. The serum of animals injected with this nucleo-protein would agglutinate the Shiga bacillus.

Horimini (341) has reported that by means of washing and neutralization he has been able to separate the toxins of the Shiga bacillus into four fractions. One attacks the cecum, another the central nervous system, another the small intestine and the fourth produces lesions in the colon.

The mannite fermenting dysentery bacilli, on the other hand, produce endotoxin but usually no exotoxin.

The divisions of the mannite fermenting (Flexner) group of dysentery bacilli

The existence of the Flexner-Harris, Strong and Y types of mannite fermenting dysentery bacilli has been confirmed (36, 80, 123) in various parts of the world and furthermore it has been shown on the basis of the differences in fermentation of other carbohydrates such as sorbite, dextrin, dulcite and rhamnose, that there are probably additional members of the mannite fermenting group of dysentery bacilli (7, 80, 124).

A tremendous impetus was given to the study of bacillary dysentery by the Great War. The publications of the workers of the Medical Research Committee of England, the Royal Army Medical College and others have placed our knowledge of the disease on a new plane. At first there was considerable confusion in regard to the different varieties of mannite-fermenting dysentery bacilli. It had previously been shown that divisions of this group into Flexner-Harris, Strong and Hiss-Russell-Y on the basis of the fermentation of maltose and saccharose were unreliable (35, 37, 56, 57, 110, 130, 222). An organism may be isolated from a patient's stool that gives the fermentation reactions of the Hiss-Russell-Y organism, i.e., not producing acid in maltose and saccharose. If the fermentations are repeated after a

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lapse of a few months, they may be identical with those of the Flexner-Harris bacillus, i.e., forming acid in maltose and saccharose. If this organism is then injected into an animal and then recovered and its fermentation ability retested, a reversion to the original Hiss-Russell-Y type may be noted (110). The question then is, what type of bacillus caused this patient's dysentery? Serological results did not always help for many Flexner-Harris and Y monovalent sera will cross-agglutinate to such high titres that it is impossible to decide which is specific. The changing fermentative ability of these divisions probably accounts for the frequent confusion of the sera, for in the example I have just quoted, a diagnostic serum made with the freshly isolated organism, while it gave fermentative reactions similar to a Y bacillus, would of course be called a Y serum. After a few months, however, if a diagnostic serum was made with the same culture which then fermented as a Flexner-Harris bacillus, would this new serum be a Flexner-Harris serum? At any rate, both the original and the new sera will agglutinate this organism that was at one time a Y bacillus and later a Flexner-Harris type, for the agglutinins of the serum do not change their type (222). If a serum reacts with a freshly isolated organism at a dilution of 1/100, it will usually react to the same or a higher titre with this organism after a few months of laboratory cultivation (431). As an exception to this, Benians (114) has just shown that injecting an agglutinable Shiga bacillus suspended in mucilage of tragacanth into a guinea pig may render it inagglutinable. This may, perhaps, be due to the same process involved in Bordet's and Ciuca's (233) experiment (bacteriophage or d'Herelle phenomenon) (vide infra). Cultivation in bouillon containing antidysenteric serum will produce the same result (115, 452). In some instances (378) long cultivation alone may decrease the agglutinability of a strain of dysentery. Werdt and Kopatschek (367) found that all strains of B. dysenteriae when grown on a protein free medium to which test sugars had been added, failed to ferment dextrose, mannite, maltose, lactose or saccharose. Other members of the colon-typhoid group produced their typical sugar reactions. Addition of a small amount of peptone to this protein free medium reëstablished the usual sugar fermentations characteristics of the dysenteries. These investigators conclude from this that dysentery bacilli do not form carbohydrate splitting

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enzymes in the absence of protein. It may be seen therefore that in the whole series of dysentery bacilli marked changes may occur or be brought about that will greatly alter both the fermentation capacity and the agglutination characteristics of these organisms. However, although the agglutinability of a dysentery bacillus may occasionally be reduced to zero, yet a distinct change from one serological variety to another does not occur, whereas a change from one fermentative variety to another is quite common within the mannite-fermenting group.

Murray (131) and others (132, 133) have attempted to clarify this question. Murray found that 34 mannite fermenting dysentery bacilli isolated from cases of dysentery in different parts of the world fell into five divisions on the basis of their agglutination reactions with monovalent rabbit sera. These five divisions were designated as the V, W, X, Y, and Z divisions of the Flexner group by a committee of bacteriologists appointed by the British War Office Committee on Dysentery. The names of the various subgroups based on differences in fermentation of maltose and saccharose have been discarded. The name Flexner* is now usually applied to the whole mannite fermenting group and the subdivisions based on agglutination noted, i.e., B. dysenteriae (Flexner, type V, etc.).

I used fermentation tests with maltose, saccharose, dulcite and rhamnose, and also agglutination tests with Murray's five (English) Flexner monovalent rabbit sera types V, W, X, Y and Z to differentiate eighty-nine cultures of mannite fermenting dysentery bacilli isolated from the stools of cases of dysentery in adults and children (132). On the basis of the fermentation tests, these cultures fell into seven groups which did not correspond with the groups obtained by the agglutination tests, i.e. of the organisms that fermented maltose and not saccharose, some were agglutinated by the Y serum and others by the Z serum. Of the organisms agglutinated by the X serum, some fermented maltose and saccharose and others did not ferment saccharose. In order to avoid this confusion either fermentation or agglutination methods must be adopted as the criterion for classification.

*In the remainder of this paper by B. dysenteriae (Flexner) or the Flexner bacillus I shall refer to the whole mannite fermenting group of dysentery bacilli.

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Agglutination tests were performed with V, W, X, Y and Z stock cultures and the sera of the patients from whose stools dysentery bacilli were obtained and a general correspondence was found between these serum reactions and the serological grouping of the stool organisms. That is, if the patient's serum agglutinated the V and Y stock cultures, his stool organisms would be agglutinated by the V and Y type sera.

As the fermentation reactions of these cultures may change after subculture and as the serological typing is fairly constant (222), a grouping on the basis of agglutination is preferable. Inasmuch as Murray studied organisms from such widely distributed sources it would seem advisable to adopt his serological classification and to add to it the types that fail to be agglutinated by his V, W, X, Y and Z sera. Polyvalent sera for diagnostic and therapeutic purposes should include antibodies for the more common of these types.

There are probably other types of Flexner bacilli in addition to the V, W, X, Y and Z types (57, 449), for from the stool of one dysentery patient I isolated a mannite fermenting dysentery bacillus that was not agglutinated by any of the five diagnostic sera and there were no agglutinins in this patient's serum for the V, W, X, Y and Z stock cultures (132).

Flexner cultures are rarely agglutinated by only one of these five sera; for example, a strain may react with the Y serum at a high titre and with the W and X sera in lower dilutions. Murray believes that there are five or more antigens in the Flexner group, one of which predominates in a given culture.

Absorption tests and the Michealis "acid agglutination" reaction (57, 134, 135) are of little assistance in the division of the Flexner group.

The toxins of the mannite fermenting (Flexner) group of dysentery bacilli

It has usually been assumed that the Flexner group of dysentery bacilli caused nothing but intestinal lesions because they only produced endotoxin, an enterotoxin, but Thjotta and Sundt (442) have reported that filtrates of eight-day bouillon cultures of one of the subgroups of mannite fermenting dysentery bacilli contained a neuro-

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toxin. When these filtrates were injected into animals, nervous lesions occurred after an incubation period, but no intestinal lesions were encountered. These bacilli also possessed an endotoxin which caused intestinal disturbances, usually of a mild character. Repeated injections of the two toxins rendered animals immune. A weak antitoxin could be prepared for each of these toxins.

Geographical distribution of Shiga and Flexner dysentery bacilli

During the war the predominating type of organism varied with the epidemic. On the Gallipoli peninsula (54), along the German and Austrian Eastern fronts (69, 71, 72, 73, 74), in Russia (136), Brittany (137), Albania (90), Macedonia (355), Norway (455), and in the recent British outbreaks (29, 356), the Shiga bacillus was usually more prevalent while the Flexner bacillus was the more common along the Western front in the Allied (69, 55) as well as in the German armies (73), along the Serbian front (70), in Salonika (222), in Brussels (415) and among the civilians in Germany, Austria (69) and South America (387). Two small Shiga epidemics have, however, recently been reported in Germany (357, 368). Flexner and Shiga infections were about equally frequent in Mesopotamia (370). Blackburn (380) states that Flexner infections were more common in Palestine.

In the sporadic cases of dysentery in children the Flexner bacillus is more common than the Shiga variety (48, 124, 138, 139, 140, 389, 418). The statement is sometimes made (140) that mixed Flexner and Shiga infections in children are more common than infection with the Shiga bacillus alone. This has not been true in our series of cases (48). In 35 cases of bacillary dysentery in children in Baltimore and Birmingham, Alabama, I found 31 due to infection with B. dysenteriae Flexner and 4 with B. dysenteriae (Shiga). I did not find any cases of mixed infection.

Intermediate or atypical varieties of dysentery bacilli

In addition to the Shiga bacillus and the various members of the Flexner group, intermediate varieties have been described (141, 389). Three of these types of dysentery bacilli deserve mention. One, a bacillus that forms acid and no gas in lactose, was called B. pseudo-

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dysenteriae type E by Kruse (34) and is colloquially known as Kruse E. There is probably a whole group of these bacilli that produce acid and no gas in lactose (39, 142, 143). Andrewes (134) calls the members of this group, B. dispar and doubts their pathological significance. There is no absolute proof that these organisms can cause dysentery but it is not at all unlikely that some of them are pathogens. Hilgers (384) isolated several strains of Kruse E from children suffering with follicular enteritis. He considered it to be identical with Sonne's group III (123). I have recovered Kruse E bacilli (68) that agglutinated with Murray's Kruse E serum in six cases of dysentery in adults and from the intestines of one fatal case of dysentery in a child, and an inagglutinable variety in six additional cases of dysentery in adults and four non-dysenteric cases in children. The sera of several normal individuals agglutinated B. dispar (Kruse E) in dilutions of 1/50.

Schmitz (76) in 1916 during an epidemic of dysentery among Roumanian prisoners isolated a new type of bacillus. This organism is non-motile, produces indol and forms acid and no gas in dextrose and rhamnose. Ornstein (365) working with eight strains of the Schmitz bacillus isolated from dysentery patients has confirmed these results. He also showed it to be distinct from B. fallax. Blumental (377) isolated the Schmitz bacillus in Galicia and considered it agglutinogenically identical with Kruse J bacillus. Andrewes calls this B. ambiguus and is doubtful, as this name implies, of its pathogenicity. Nevertheless it produces dysentery (57). A laboratory technician (144) pipetted a mouthful of culture of the Schmitz bacillus and developed mild dysentery two and a half days later. The Schmitz bacillus was recovered from the stools. Broughton-Alcock (145) recovered this bacillus in two outbreaks of mild dysentery among British troops. Kirschner and Segall found it in cases in Vienna (406). I have recovered it in two cases during an epidemic of dysentery in the A. E. F. (68). No serum that I have tested either from dysentery patients or from normal individuals has agglutinated the Schmitz bacillus in dilutions of 1/20. Somewhat similar organisms have been isolated by other workers (124, 140, 146, 389) and called by various names such as "alkaline" or pseudodysentery bacilli. Flexner believes them to be non-pathogenic (39).

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A third organism called B. alkalescens by Andrewes is a mannite fermenting bacillus differing from the Flexner group in that it forms acid (no gas) in dulcite. Three of the four strains that I have encountered in cases of dysentery have not been agglutinated by any of the Flexner type sera. I have not recovered B. alkalescens from normal individuals. The biological characteristics of these various organisms are expressed in table 1.

TABLE 1

Biological characteristics of the various types of dysentery bacilli

TYPE OF BACILLUS	GRAM STAIN	MOTILITY	INDOL	GELATIN	LACTOSE	DEXTROSE	MANNITE	MALTOSE	SACCHAROSE	DULCITE	RHAMNOSE	XYLOSE
B. dysenteriae (Shiga).....	0	0	0	0	0	+	0	Var	0	0	0	0
B. dysenteriae (Flexner)...	0	0	Var	0	0	+	+	Var	Var	0	Var	0
B. dysenteriae (Kruse E) or B. dispar.....	0	0	Var	0	+	+	+	+	+	0	+	+
B. dysenteriae (Schmitz) or B. ambiguus.....	0	0	+	0	0	+	0	0	0	0	+	0
B. alkalescens.....	0	0	+	0	0	+	+	+	0	+	0	−

+ indicates formation of indol, or production of acid and no gas in carbohydrate media.

0 indicates negative gram staining, non-motility, non-indol production, non-liquefaction or non-fermentation of carbohydrate media (twenty-eight-day incubation).

Var (variable) indicates that some members of the group form indol or produce acid and no gas in carbohydrate media while other members fail to do so.

− indicates that a test was not made.

Acid production by dysentery bacilli

Zoller and Clark (416) have shown that under aerobic and anaerobic conditions, in the presence of 1 per cent dextrose, Shiga, Flexner, typhoid and paratyphoid bacilli produce approximately the same total amounts of volatile fatty acids and about the same proportions of formic and acetic acids. When these organisms are grown aerobically on sugar-free peptone water, volatile fatty acids are formed in appreciable amounts. Formic acid, however, is not produced but propionic acid is found in its place. When cultured anaerobically on non-sugar media, these bacteria produce formic acid and also a certain amount of butyric acid. Zoller and Clark suggest that the enormous amounts of formic acid produced by these bacilli may

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play a significant part in causing the digestive disturbances and toxic symptoms accompanying their infection of the human gastro-intestinal tract.

Mutation of dysentery bacilli

A certain amount of mutation can be produced in dysentery bacilli. Fletcher (147) has isolated bacilli from the stools of a dysentery carrier and of a convalescent patient that were apparently capsulated and that formed mucoid colonies. Organisms resembling dysentery bacilli (mannite-fermenting) were obtained by plating out peptone water cultures of these mucoid bacilli. These organisms were agglutinated by dysentery serum but did not absorb agglutinins. Maymone (148) reported that Shiga bacilli isolated from the stools of the same patient might differ in agglutinability, absorption and dextrose fermentation.

Arkwright (38) from a single strain of B. dysenteriae (Shiga) as well as from single strains of several different members of the typhocoli group, has obtained two forms. One of these made a stable emulsion in physiological salt solution and the other yielded an emulsion which was spontaneously agglutinated in normal saline (without the addition of serum). These two types were also distinguishable by the difference in their growth. Both of these variants of B. dysenteriae (Shiga) were agglutinated to the same titre by a stock Shiga serum. Sera, made by immunizing animals with each type, however, agglutinated only their homologous strains in high dilutions and showed but very slight cross-agglutination. De Kruif (435) has had somewhat similar results with the organisms of rabbit septicemia.

Twort (348) reported that repeated subcultures of young Shiga cultures eventually showed a preponderance of large thick bacilli. When these were grown anaerobically, and then subcultured aerobically, two types of colonies resulted, A, a large mottled colony composed of waxy long spirochaete like bacilli containing a few granules and B, a gray colony which later became mottled and was formed by long bacilli with swollen ends, some of which appeared to split open and to liberate free granules. When type B colonies were replated, a third type of bacillus was found. These type C organisms were shorter, thick bacilli and they formed waxy colonies. The A, B and

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C types gave rise to mixed forms on subculture but they did not revert to their original form. Cultures of the A, B and C types were agglutinated by Shiga serum to higher titres than the original Shiga culture, but spontaneous agglutination was frequent. Type C produced a large amount of acid in maltose, type B formed a fair amount, while type A produced little or none. Twort suggests that these different types represent sexual forms, or that each type has a special function such as toxin production, food production, reproduction, etc. They do not represent a life cycle as they do not revert to their original form.

It is possible that this mutation depends upon the same process that is responsible for the changes in the form of the colonies and in the characteristics of the bacilli that are seen in dysentery cultures which have been acted upon by bacteriolytic filtrates (bacteriophages, d'Herelle phenomen). This will be discussed later.

Relation of length of disease to excretion of dysentery bacilli

It is frequently stated (56, 63, 64) that after the sixth day of the disease in adults it is impossible in the majority of cases to isolate B. dysenteriae even though the stools contain mucus. The percentage of positive stool cultures in typical cases of bacillary dysentery is rarely high (69, 74). Seligman (69, 71) found B. dysenteriae in 38 per cent of all of his acute cases. His highest percentages were in the first few days of the disease (see table 2). Martin and Williams (56) have made an interesting analysis of their 1050 positive stool cultures in cases of dysentery among the Mediterranean Expeditionary Force. Only 15 per cent were positive at the first examination. This emphasizes the necessity for repeated cultures and that single negative examinations are worthless. The earlier in the disease the cultures are made, the higher the percentage of positive results (see table 2), which is somewhat different from the experience with typhoid fever. However, occasional patients excrete the organisms for months (69) and even years (174). Fletcher and MacKinnon (175) have applied the term persistent carriers to individuals harboring dysentery bacilli over three months. Many of them cease to have clinical symptoms of dysentery.

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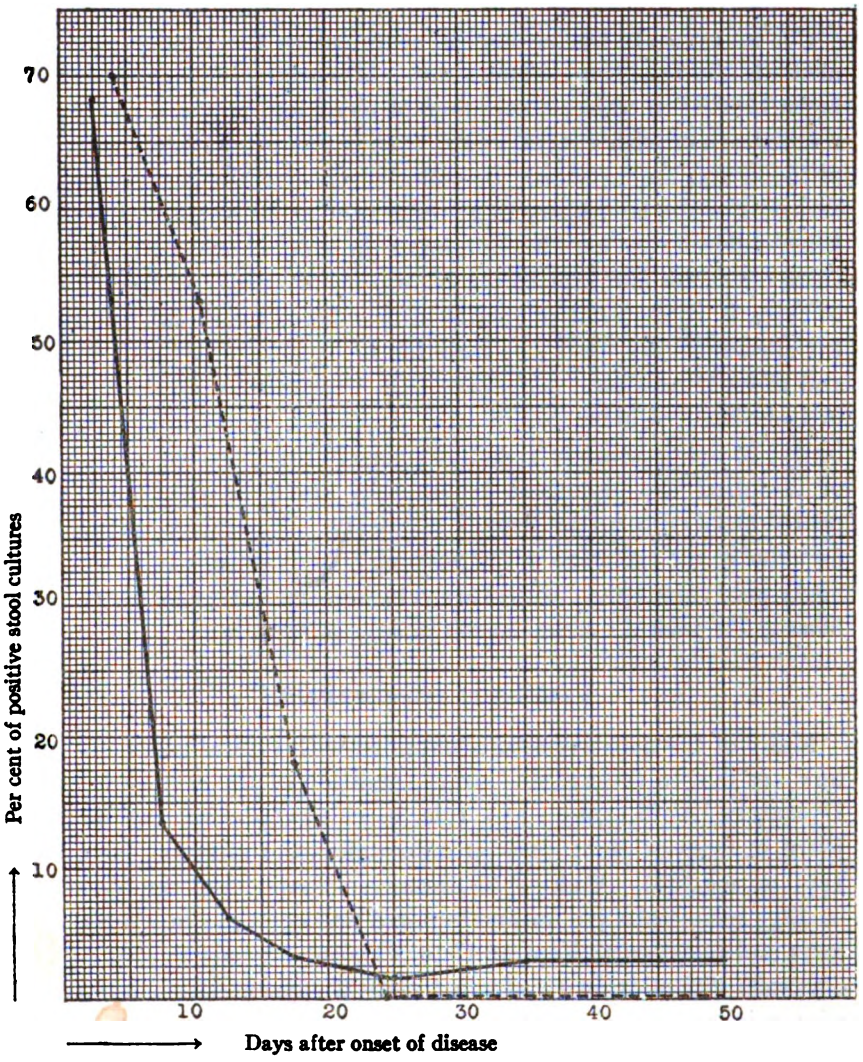

TABLE 2

Graph represents success in recovering dysentery bacilli from the stools at different periods after the onset of the disease. ——— figures from 1050 cases (Martin and Williams) (56), ------- figures of Seligmann (71)

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Collection of stool specimens

For an accurate bacteriological examination the proper collection of stools is of the utmost importance. It is preferable for the bacteriologist himself to collect a specimen of blood and mucus directly from the bed pan or with a rectal swab. When this is impossible, a portion of blood and mucus should be collected on a sterile swab or spatula and sent to the laboratory in a sterile tube or jar as soon as possible. With children, the napkin containing the stool should be placed in a clean container and sent to the laboratory at once. In the majority of cases B. dysenteriae is greatly outnumbered by B. coli and unless the specimens are fresh, the isolation of dysentery bacilli is difficult and often impossible. Friedman (125) suggested that the difficulty in isolating dysentery bacilli from dysenteric stools might possibly be due to the presence of a bacteriophage in the specimen which killed or inhibited the organisms before they could be cultivated. Repeated stool cultures are usually necessary. A negative culture is of no value in the exclusion of the possibility of dysenteric infection. In many mild cases stool cultures are valueless and the *agglutination reactions of the patient's serum should always be performed.*

Viability of dysentery bacilli

Many of the negative results obtained with typical cases of dysentery are due to the age and dried condition of the stool specimens. Dysentery bacilli cannot, as a rule, be cultivated after two days sojourn in feces or eight days in milk unless the mixtures have been kept on ice (34). Pfuhl (176), however, found that the dysentery bacillus remained alive for one hundred and one days in a mixture of feces and moist earth kept at 1° to 5°C. but for only twelve days in dry soil. Schmidt (450) claimed that B. dysenteriae survived all winter in moist soil. Kligler (448) found that Flexner dysentery bacilli survived eight days in feces, seventy days in moist soil and eight days in the fluid from a septic tank when the reaction was between pH 7.4 and 7.8 but only three days at pH 8.6 or over, They could not be cultivated after twenty days in dry soil and ten days in acid soil (pH 5–5.5). I have alternately frozen and thawed a saline suspension of Flexner bacilli once daily for thirty-three days and

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found that the organisms remained alive (395). Lauber (368) found that dysentery bacilli soon died out in stools kept at 37°C., becoming overgrown by B. proteus; in the ice box, however, specimens remained positive for B. dysenteriae for as long as ten days. Organisms may survive in dry feces twelve days, in soiled linen nineteen days, in water, in butter, and in cheese nine days (57, 176, 322). I have found that a peptone water culture of Flexner bacilli remained alive after one hundred and fifty two days at 37°C. The bacilli are killed in half an hour by one per cent carbolic acid and immediately by 5 per cent carbolic and 1:2000 solution of corrosive sublimate (39). B. dysenteriae is usually killed by being kept at 0°C. for two months and also by being heated to 60°C. for ten minutes (180, 222). The thermal death point however may vary with different strains. Direct sunlight is said to kill this organism in thirty minutes (222). Stools of dysenteric patients are usually markedly acid in reaction. With increasing acidity of the stool it becomes more and more difficult to find dysentery bacilli by bacteriological methods (371, 382). In Salonika (57) it was found that by mixing equal parts of 3 per cent sodium hydroxide with the specimen the viability of dysentery bacilli was increased so that stool cultures were satisfactory twelve hours after the collection of the specimen.

Technique of stool cultures

A loop full of bloody mucus (unwashed) is streaked over the surface of one Petri plate of Teague's or Endo's medium and then without flaming the loop, it is streaked over another plate. This will usually result in separate discrete colonies on the second plate. I have found Endo's medium (48) satisfactory but now prefer Teague's medium (177,178, 179) of methylene blue eosin lactose agar, as the differentiation of B. coli and B. dysenteriae is more definite. English investigators recommend McConkie's Bile Salt agar (180).

After eighteen hours incubation at 37.5°C. the colorless typhoid-like colonies are fished into tubes of Russell's double sugar medium (178, 180, 181) (Andrade's (182) indicator). Those cultures that have colorless slants and red butts without gas after eighteen hours incubation are subcultured into gelatin and seven Durham fermentation tubes of peptone water containing respectively 1 per cent of lactose, dextrose, mannite, maltose, saccharose, dulcite and rhamnose (brom-cresol purple indicator) (183). The first three carbohydrates are the most essential.

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The growth from the original culture (Russell's slant) is then emulsified in saline and agglutinated macroscopically at 55°C. for five hours with polyvalent dysentery, Flexner and Shiga type sera. Six to eight hour peptone water cultures are examined for motility and seven-day peptone water cultures are tested for indol by ether extraction and Ehrlich's reagent (48, 184).

The fermentation cultures are read at intervals for over fourteen days and the gelatin cultures are left at room temperature for twenty-eight days.

The necessity for prolonged incubation of fermentation cultures is shown by the fact that 12 per cent of the cultures from children in our series (48) and 29 per cent of those from the series in adults (68) were late lactose fermenters, that is, formed colorless colonies on Endo's or Teague's medium but fermented lactose after the second day of incubation. All fermentations were practically complete by the 14th day and only very slight changes occurred during the remaining time of the twenty-one day incubation. It would seem that fourteen days incubation for fermentation cultures is sufficient.

Subsequent agglutination work to confirm the original tests or to determine the V, W, X, Y or Z type if the culture ferments mannite is done (macroscopically) with eighteen-hour peptone water cultures.

Agglutination reactions of the patient's serum

Inasmuch as the isolation of dysentery bacilli from the stools requires considerable time as well as training, the agglutination reactions, which are positive after the sixth to the tenth day of the disease, are frequently used in the diagnosis of dysentery. It is often stated that the patient's serum reactions in dysentery are uncertain (46, 70, 185, 186, 187, 222, 356, 385). It is just as commonly claimed that they are of the greatest value (48, 69, 71, 72, 73, 150, 154, 184, 188, 189, 368, 409) and that the serum of normal individuals does not agglutinate B. dysenteriae (190).

The confusion in regard to the reliability of the diagnosis of bacillary dysentery by agglutination is largely due to two things; first that there are five or more types of the Flexner bacillus and if any of these types are omitted in agglutination tests, the sera of some dysentery patients which may agglutinate one of these omitted types, may be reported as negative (48, 57); and second because living cultures are

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frequently employed as antigens (191, 222). Living cultures vary from time to time in their agglutinability (114, 115, 192, 193, 194, 195, 431). Therefore agglutination tests made with dysentery cultures killed by formol (standard agglutinable cultures) whose agglutinability does not vary, are much more reliable. It is of the greatest importance that only those dysentery cultures whose sensitiveness to agglutination has been thoroughly tested should be selected for the preparation of "standard agglutinable cultures." Many strains even of the same serological type as the organism producing the patient's disease are not agglutinated by the patient's serum. On the other hand, dysentery cultures are frequently encountered which are agglutinated to comparatively high titres by the sera of normal individuals. Some investigators (196) have, it is true, reported unsatisfactory results with Dreyer's formolized cultures, but the majority find the method extremely useful. Employing the technique outlined below, I have found that agglutinins in a patient's serum in a dilution of 1 to 30 or over, are usually diagnostic of previous or present dysentery infection. In all patients in our series (48) from whom an agglutinable B. dysenteriae was recovered and whose sera were tested, specific agglutinins were found. Very rarely the sera of typhoid patients or of normal children and adults with no history of dysenteric infection will give positive dysentery agglutination reactions. There is evidence to prove that non-specific agglutinins may be present in the sera of typhoid patients (197, 198, 199). Occasionally the serum of patients with dysentery may agglutinate B. paratyphosus B (379).

Agglutinins for B. dysenteriae are usually demonstrable after the sixth day of the disease, although they are occasionally reported earlier (38, 200). The serum of one child was positive on the second day (48), the titre rising on the fourth (198) and ninth days. The maximum titre is probably reached on the seventeenth to twenty-first day as it is in typhoid fever (57). The titre of a dysentery patient's serum for dysentery bacilli is practically always lower than that of a typhoid patient's serum for typhoid bacilli, probably because dysentery bacilli are usually less agglutinable than typhoid bacilli. A dilution of 1 to 250 especially in Shiga infections is the usual limit at the height of the disease (seventeenth to twenty-first day) but in a few cases of

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Flexner infection I have found agglutination for the Flexner bacillus as high as 1 to 1000. However, these titres depend upon the agglutinability of the cultures used in the test. Agglutinins may persist longer than four months. In the sera of four children tested after six months they were still present (48, 57, 69). Agglutination for both Shiga and Flexner groups is occasionally found in single infections with either one of these bacilli (55,.57, 69, 201). I found this in two of our cases (48). True double infections with both Flexner and Shiga types have, of course, been reported (57, 69, 138, 140, 202).

Agglutination technique

I have obtained consistent results with Dreyer's technique (48, 194, 203) but inasmuch as I have used eleven different antigens I have adopted the following modification of this method for all routine agglutination tests in diarrhoeal diseases:

One cubic centimeter of the patient's serum is diluted ten times. 0.5 cc. (or 10 drops) of this diluted serum is placed in each of 11 agglutination tubes, 0.5 cc. (or 10 drops) of a formolized standard agglutinable culture of each of the following organisms is each placed in one of these 11 tubes: B. typhosus, B. paratyphosus A, B. paratyphosus B, B. shigae, B. dysenteriae (Flexner), English types V, W, X, Y, and Z, B. dysenteriae (Kruse E) or (B. dispar) and B. dysenteriae (Schmitz) (or B. ambiguus). In localities where other types of pathogenic intestinal organisms, such as atypical paratyphoid bacilli (69, 204, 205, 206, 207) (Salonika, Bagdad and India) or B. Gaertner (208) are common, they should be added to the series.

These tubes are incubated in a water bath at 55°C. for four and one-half hours. If agglutination is positive for any of these 11 antigens at this 1 to 20 dilution, tests are set up according to Dreyer's directions, using only those standard agglutinable cultures for which there have been agglutinins in the preliminary test.

Blood cultures

Blood cultures, as a general rule, are of but little assistance in cases of dysentery for only in rare instances do dysentery bacilli enter the blood stream. Tenbroek (209), Schloss (210) and others (188, 211, 212, 218) have reported occasional positive antemortem blood cultures for B. dysenteriae. Caussade and Marbais (213) found the Shiga bacillus in the blood stream of one patient although stool cultures were negative.

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Dysentery bacilli have been found in a few instances (37, 57, 140, 188, 214, 215) in the heart's blood, mesenteric glands and spleen at autopsy but such findings are the exception (138). Recently positive blood cultures of B. fecalis alkaligenes (216) have been reported in a few cases of bloody diarrhea in children, as well as in an adult with a typhoid like disease (432).

Urine cultures

In one child with bacillary dysentery we found (217) typical B. dysenteriae (Flexner) in the catheterized urine. Fraenkel (218) cultured the urine of 39 patients with mild bacillary dysentery and found B. dysenteriae (Flexner) in three. In the urine of another patient B. dysenteriae and B. typhosus were associated. Sonne (123) reported the presence of Flexner bacilli in the urine of a typhoid convalescent and others have occasionally found bacilli morphologically and culturally indistinguishable from B. dysenteriae in the urine of patients with pyelocystitis (219) and other diseases (218, 220) but proof that all of these urinary organisms were true dysentery bacilli was not brought forward.

The infrequence of positive cultures of B. dysenteriae in the blood and urine renders the taking of blood and urine cultures of little or no diagnostic assistance.

Bacteriological diagnosis (summary)

The highest percentage of positive cultures of dysentery bacilli is obtained from culturing the postmortem scrapings of the mucous membranes of the ulcerated intestines of patients, both adults and children, dying of dysentery. Frequently over 80 per cent of these cultures are positive. The next highest percentage is obtained by culturing the bloody mucus of the feces of children with dysentery; from 50 to 60 per cent of these cultures are positive if cultures are made from several specimens during the height of the disease (from the fourth to fourteenth day). It has been reported (221, 405, 406) that the diagnosis of dysentery is rendered easier by the examination of the rectal mucosa and by obtaining cultures directly from the intestinal ulcers of adults, infants and young children by means of a

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proctoscope. However, perforation of the intestine and death from peritonitis has occurred from the use of a sigmoidoscope (446). The lowest percentage of positive stool cultures is obtained in adults (56, 69, 71); 25 to 40 per cent of the cultures of the feces of adults with dysentery may be positive if cultures are repeated during the height of the disease (up to the fourth week).

These percentages of positive cultures of dysentery bacilli are usually only obtained under ideal conditions, i.e., fresh fecal specimens that have not been allowed to become dry and an experienced bacteriologist with good media. Frequently the percentage of positive stool cultures is not sufficiently high to be of great assistance in clinical diagnoses, for even repeatedly negative stool cultures do not rule out the presence of dysentery. Moreover, two to three days are usually required for stool cultures. However, after the sixth to the tenth day of the disease a method is available that is more rapid and that is positive in practically all cases of dysentery and negative in practically all non-dysenteric cases. The agglutination reactions of the patient's serum fulfill all of these conditions after the sixth to the tenth day of the disease in adults and are frequently positive in low dilutions on the fourth day of the disease in children. As I have pointed out, this method is reliable with standardized technique and should be used as an aid to the diagnosis of all diarrheal disease. If the agglutination reaction of the patient's serum is positive for any of the dysentery bacilli, a diagnosis of past or present dysentery (or of prophylactic vaccination) can be made. The exceptions to this are infrequent. If the agglutination reaction is repeated quantitatively after an interval of four days and a marked increase or decrease in the titre of the serum is present, a diagnosis of active dysentery can be made as the titre of the serum of patients who have had dysentery some time previously or who have received prophylactic inoculations of vaccine soon reaches a constant level and tests made at short intervals will show no change. If the agglutination reaction of the patient's serum is negative for all of the dysentery bacilli, the disease can usually be ruled out but the test should be repeated two or three days later.

For a bacteriological diagnosis before the sixth day of the disease stool cultures are necessary. If negative, they should be repeated.

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III. FILTERABLE "SUBSTANCE" ANTAGONISTIC TO THE DYSENTERY BACILLUS (D'HERELLE'S PHENOMENON, BACTERIOPHAGE, BACTERIOLYTIC AGENT, BACTERIOLYSANT, ETC.)

Under these names, which have been used interchangeably, an extensive literature has accumulated in regard to a "substance" contained in filtrates of stool cultures and also obtained from other sources which when added to young cultures kills and dissolves dysentery bacilli and other organisms. It has usually been assumed that Twort (126) was the first to describe this phenomenon though Hankin (426) in 1896 demonstrated that the water of the Ganges and Jumna rivers in India was bactericidal for bacteria in general and for the cholera vibrio in particular. Inasmuch as heating the water to 115°C. for a half hour (a temperature which destroys bacteriophagic activity) did not totally destroy its bactericidal activity, Hankin was probably not dealing with a bacteriophage. Nicolle (425) in 1907 reported that cultures or filtrates of B. subtilis would dissolve pneumococci, staphylococci, B. typhosus, B. coli, V. cholerae and B. shigae. Though not recognized as such, this is perhaps the first mention of "bacteriophagy."

Source

There have been at least five methods described by which a bacteriophage may be obtained.

1. Twort (126) in 1915 noted in a culture of staphylococci obtained while plating out glycerinated calf vaccine, transparent areas in which no cocci grew or if they had grown, they had become degenerated. If one of these transparent areas was touched with a sterile platinum loop and the loop was then drawn (without flaming) across the surface of a twenty-four hour agar culture of staphylococci, a streak marking the track of the loop became clear and transparent within a few hours. He then passed the material from these transparent areas through a Berkfeld filter and found that it would dissolve and kill most of the organisms in fresh staphylococcus agar cultures even when diluted one to a million. This bacteriolytic property could be passed on to numerous generations by adding a filtrate to successive fresh staphylococcus cultures and then refiltering. Gratia (376) has recently confirmed Twort's work.

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2. D'Herelle (125) in 1917 inoculated two to three drops (or a piece the size of a pea) of a stool from a convalescent dysentery patient in 20 cc. of broth and filtered this culture through a Chamberland No. 12 filter. A trace of this filtrate would dissolve and kill broth or agar cultures of B. shigae. A loopful of the filtrate obtained by filtering this dissolved culture through a Chamberland filter would again dissolve a fresh culture of B. shigae. By similar methods bacteriolytic filtrates active against various strains of organisms have been obtained from the urine of a convalescent dysentery patient (125), from the urine of patients with pyelonephritis (125), from the stools of patients suffering from dysentery (125, 391, 392, 395, 397), typhoid and paratyphoid fever (125, 392, 394), gastric carcinoma (392), rheumatic fever (392), pthisis (392), peritonitis (392, 397), and diarrhea (126, 395), from the stools of cases of avian typhoid in chickens (125), of hemorrhagic septicemia in cattle (125), of plague in rats (125), of flacherie in silk worms (125), of distemper in dogs (126) from the blood of white rats fed on typhi murium (125), in Paris city water (391), in water from the Seine (391), in earth (391) as well as from the stools of normal adults (125, 391), children (395) and animals (125, 391).

3. Bordet and Ciuca (233) injected a culture of B. coli intraperitoneally into a guinea pig. The day after the third injection they found that a small quantity of the resulting peritoneal exudate as well as the culture of B. coli isolated from this exudate would dissolve an eighteen-hour culture of the strain of B. coli that had been used for these inoculations. This lysis was not complete and a few colonies could be cultivated. If these surviving organisms were inoculated into another eighteen hour colon culture, lysis would again result. This bacteriolytic action could in this way be repeated indefinitely. The bacilli exposed to the lytic substance acquired the ability to transfer the lytic property to subsequent generations. Wollstein (397) repeated this work using a strain of the Shiga bacillus instead of B. coli and obtained a bacteriophage active against dysentery and other bacilli.

4. Kuttner (394) found that a filtered glycerine extract of the small intestine of a guinea pig and a saline extract of a guinea pig's liver were bacteriolytic for typhoid bacilli. This lytic principle could be trans-

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mitted by passage through successive typhoid cultures. Glycerine extracts of the large intestine and of muscle tissue were not bacteriolytic.

5. I found that if one to sixty day old broth or peptone water cultures of recently isolated or old laboratory strains of B. dysenteriae (Shiga) or (Flexner) were filtered (395), the filtrate in many instances was slightly bacteriolytic against Shiga and Flexner bacilli. Bacteriolytic substances have been reported by others in cultures of B. dysenteriae (126, 397, 438) and D. mucoides (423).

Non-specificity of bacteriolysants

Originally it was thought that the lytic action of a filtrate was specific (125, 126, 233) and that only the organism producing it or causing the patient's infection would be attacked. Later it was reported (125, 429, 376) that no two bacteriophages were alike, some were active against several species of bacteria, others only against one. At present it is believed that all bacteriophages can be made practically omniverous by adding them to cultures of other bacilli, incubating and then filtering the preparation. This may have to be repeated several times before the filtrates will lyse the organism with which it is being cultivated. In this way "bacteriophagy" has been extended to several stains of the following groups, Shiga, Flexner, typhoid, paratyphoid A and B, colon, proteus, hog cholera, etc. (125, 233, 376, 395, 397). Other organisms such as Friedlander's bacillus, B. avisepticus, B. Morgan, etc. have been tested with negative results (397).

Variations in the titre of bacteriophagic activity

Some filtrates may cause lysis when diluted over a million times while others are only active after passage through several successive cultures. The potency of the lytic principle of subsequent generations of filtrates may vary, however, in some being greater than that of the original filtrate (125) in others less (395) and in others the same (394). The lytic power of filtrates which have become contaminated by air or stool bacilli and have been refiltered are sometimes greater and sometimes less than that of the original uncontaminated filtrate (395). Filtrates obtained from the stools of a dysentery patient were some-

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times more and sometimes less active against the dysentery bacillus isolated from that patient than against other strains. The bacteriolytic power of a filtrate may vary for different subcultures of the same strain, for cultures isolated from the same patient at different stages of the same disease (125, 395) as well as for subcultures of different colonies fished from the same stool culture (395). The greater the concentration of the bacteriophage, the more rapid and complete is the bacteriolysis (125, 395), i.e., a filtrate which dissolved a culture in three hours when diluted 1:10 usually required 12 hours when diluted 1:100 (394). There are evidently two steps in the d'Herelle phenomenon, first, the organisms are killed and second, they are dissolved. If there were more than 500 million bacteria per cc. only the first step occurred (125). This may possibly be due to the fact that the bacteriolytic principle is adsorbed by the more concentrated bacteria. I found (395) that broth cultures of Flexner bacilli which contained 100 million bacilli or more per cubic centimeter at the commencement of the experiment contained less than 30 viable organisms per cubic centimeter after twenty-four hours contact with an anti-Flexner bacteriolysant. The number of bacteria killed was usually proportionate to the amount of bacteriolysis. There is evidently an optimum concentration of bacteria for if the numbers present were very small, they were destroyed more slowly than when in large numbers (438).

Factors influencing bacteriophagic activity

Temperature. The lytic power of a filtrate is destroyed by being heated to 75°C. for a half hour (127, 394). It is still active after one hour at less than 0°C., four years at 37°C. (127), one hour at 64°C to 65°C., or a half hour at 70°C. (127, 394), though its power may occasionally be diminished by these two latter temperatures (395). The rate of lysis was twice as rapid in a culture and bacteriophage incubated at 41° to 42°C. than at 37°C. (394): at 15° to 16°C. it proceeded very slowly (125) and did not occur at all when the incubation temperature was from 45° to 50°C. (394).

Reaction and oxygen supply of the media. Gratia (376) showed that the inhibition by the lytic agent on the growth of B. coli was slight at pH 6.8, 7.0 and 7.4 but much more pronounced at pH 8.0 and 8.5. Lysis was more complete at pH 8 and 8.2 than at pH 6 to 7.7 (395).

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A bacteriophage was active in media with reactions from pH 2.5 to 8.4 but lost its power when the hydrogen ion concentration was above pH 2.5 and below 8.4 (424). Wollstein (397) reported that the lytic action proceeded as rapidly and as completely in the absence of oxygen as in its presence.

Chemicals. A substance having bacteriolytic power has been precipitated from filtrates by the addition of acetone (127), alcohol (127) ammonium sulphate and tricalcium phosphate (439). Kabeshima (127) reported that the lytic agent was soluble in ether and that the addition of 1 per cent sodium fluoride would not destroy the lytic power of a filtrate but both statements have been denied (125, 128). Bablet (128) claimed that glycerine and chloroform inhibited lytic activity. Eliava and Pozerski stated that twenty-four hours' contact with 2.5 per cent phenol or 2.5 per cent sodium fluoride did not affect a bacteriophage but that 0.75 per cent quinine chlorhydrate reduced the lytic activity of a filtrate and that 1.0 per cent destroyed it. De Poorter and Maisin (439) reported that the lytic agent was destroyed by phenol and certain metallic salts and that it was insoluble in animal and plant fats and lipoids. Lytic activity was destroyed by the addition of N/5 sodium hydroxide (395). Four per cent collodium membranes were impermeable to bacteriophages (422).

Other factors. Young living cultures are essential for the action of a bacteriophage (125). Two to eight hour cultures are the most sensitive (394, 395, 397). Dead cultures are unaffected (125, 395). Although young organisms suspended in bouillon peptone water or serum are lysed, saline suspensions are not affected (233, 391,392, 394) unless the reaction is near the optimum (395). A bacteriolytic filtrate loses its power after three or four passages in sterile broth (125, 126, 392) or peptone water (395).

Separation of cultures into "resistant" and "sensitive" types by the action of bacteriophages

When a lytic strain of organisms or a culture that had been attacked by a bacteriophage was plated on agar, two types of colonies appeared (125, 233, 376, 394, 395, 397, 424, 428). These two types were also noted in a culture of a stool of an infant with dysentery (397), as well as in platings of peptone water cultures of normal Flexner bacilli

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(395). One was regular and round, resembling a typical colony of the organism. Subcultures of these always gave rise to round colonies. They were not readily dissolved by the lytic agent and were designated the "R" or resistant type. The other colonies were irregular in outline and had a "moth eaten" appearance. They were readily lysed by the lytic culture and were spoken of as the "S" or sensitive type. Subcultures of these gave rise to both regular and irregular colonies.

The resistant strains of Shiga bacilli were composed of regular, equally sized and evenly staining bacilli with some larger forms but few if any coccoid or swollen round forms. Threads were seen in older cultures of the "R" type (397). They grew slowly (376). Broth cultures were not uniformly cloudy and the bacilli rapidly sedimented to the bottom of the tube (424). Resistant organisms were practically inagglutinable and very virulent (125, 233, 276, 397). The "R" type of B. coli was extremely motile, decolorized neutral red and was only slightly phagocytable (376). D'Herelle (125) stated that resistant forms might become coccoid and acquire capsules. Resistant forms may lose their resistance after subculture (125, 428).

The sensitive strains of Shiga bacilli were composed of short bacilli and many coccoid and round swollen forms (397). The "S" type of B. coli grew rapidly in artificial media, was non-motile and did not decolorize neutral red (376). The filtrates of sensitive cultures usually had bacteriolytic power (395, 397) while only a few of those of resistant organisms were active (428). These lysogenic resistant strains might afterwards lose their lysogenic power (428). Sensitive bacilli might gradually die out after repeated subcultures (397) though Bordet and Cuica (233) found that lysogenic colon bacilli retained their lytic power even after 150 transfers.

Gratia (376) isolated eleven types from the original Bordet strain of B. coli that differed in resistance, motility, mucoid growth, ability to yield mucoid growth, fluorescence and sero-agglutination. All of these types produced indol and fermented carbohyrates except saccharose.

There is a striking similarity between the various types of organisms that may be obtained from a culture as a result of the action of a bacteriophage and those that have been described as occurring spon-

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taneously or as the result of changes in environment (vide supra, Mutation of dysentery bacilli). Inasmuch as strains closely resembling resistant and sensitive types may be obtained in platings of aged cultures (376, 395) and in cultures of B. coli of different motilities (376), it is probable that this separation of a culture into various types is a result of several independent factors rather than of the action of a bacteriophage.

Results of inoculation of bacteriophages in animals

The injections of bacteriolytic filtrates into rabbits (125, 127, 233, 395, 428, 429) and into the larvae of the beeswax moth (129) have demonstrated that bacteriophages were non-pathogenic and that animals and larvae became immunized to the organisms against which the bacteriophage was active (125, 127, 233, 395). After injection into an animal, the bacteriophage persisted in the intestine for several days (454). The rabbit sera would agglutinate these organisms (395, 397) and were also antilytic, i.e. would precipitate a lytic filtrate (233, 395, 453) and when added to a bacterial suspension and a bacteriophage (even bacteriophages other than the one used in the production of the antilytic serum (429)) would prevent lysis for at least forty-eight hours (125, 233, 438). The sera of animals immunized with lysogenic cultures were also antilytic, though sera produced by the injection of normal organisms had little (438) or no such power (233). Treatment of lysogenic colon cultures (233) and of resistant forms (428) with antilytic sera caused the former to become resistant and to lose their lytic power and the latter to lose their resistance. However, the colon bacilli that had lost their lytic activity became lysogenic again after twenty-one transfers on culture media (233). An antilytic serum apparently had an "anti-immunizing" effect for a mouse injected with one-tenth of a lethal dose of Shiga toxin plus 0.2 cc. of an antilytic serum died in thirty hours. Control mice inoculated with full lethal doses died in four days (125).

It would seem possible that the properties acquired by the sera of these inoculated animals are not due to the antigenic effect of the bacteriophage per se but are a response to the injection of the proteins of the dissolved bacteria although this has been denied (422). The anti-lytic power of the serum is probably a response to the injection

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of the bacteriolytic ferment which the filtrate contains and is perhaps comparable to the anti-tryptic power of serum of animals inoculated with trypsin. The immunization of rabbits with anti-Shiga bacteriophages (125, 127) is perhaps due to the formation of dysentery antitoxin, for a bacteriophage obtained by the lysis of Shiga bacilli contains Shiga toxin for several days (127).

Bacteriolysants as therapeutic agents

It was obvious to many observers (125, 395, 397) that this filterable "substance," which would kill and dissolve dysentery and other organisms in vitro, was non-pathogenic and would immunize animals, should be tried therapeutically. D'Herelle (125) reported that in seven cases of severe dysentery in children, three and one-half to twelve years of age the ingestion of 2 cc. of an anti-dysenteric bacteriophage was followed in from twenty-four to thirty-six hours by the disappearance of blood and bacilli from the stools. Friedmann (125) was unable to confirm this. D'Herelle also reported striking therapeutic and prophylactic benefit from the ingestion and injection of 0.25 cc. to 1 cc. of appropriate bacteriophages in epidemics of avian typhoid in chickens, plague in rats and hemorrhagic septicemia in cattle. He stated that the intravenous injection of 500 cc. of blood from one of these inoculated cattle would protect another animal from a lethal dose of living organisms. It is difficult to reconcile this result with his earlier work on the "anti-immunizing" effect of the serum of a rabbit inoculated with an anti-Shiga bacteriophage.

I have treated twelve children two months to four years of age suffering from Flexner dysentery with bacteriolysants which were tested and found to be active against the organisms causing the patients' infections (395). In this small series, even though I administered amount of 5 to 1381 cc. by rectum, by mouth or by nasal tube into the stomach, I was unable to observe the slightest benefit or harm from bacteriophagic therapy. It would seem probable that these large amounts in young children would be as beneficial as the ingestion of 2 cc. which d'Herelle found so efficacious in older children. Larger series alone will demonstrate the practical value of bacteriolysants.

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As a matter of fact although it has been frequently proven to be harmless in animals with various infections it is theoretically difficult to explain why the administration of an anti-dysentery bacteriophage to dysentery patients is not harmful. The intestinal lesions of dysentery are due to endotoxin (119) and it would seem probable that if the dysentery bacilli in the intestinal tract were lysed as a result of the administration of a bacteriophage, a large amount of endotoxin would be liberated.

Theories in regard to the nature of bacteriophages

There are at least five hypotheses advanced to explain the nature and mode of action of bacteriophages;

1. D'Herelle (125), inasmuch as he was able to preserve his bacteriophages for over a thousand successive transfers from one Shiga culture to another with no diminution of the strength of the lytic agent (in fact the lytic power increased) believed it must be a living culture and not a ferment. This culture he called the "microbe filtrant bacteriophage" or "bacteriophagum intestinale." He reported that the clear bare areas, which were noted when a bacterial suspension to which a bacteriophage had been added, was plated out on agar, were proportional to the amount of bacteriolytic filtrate added to the preparation and not to the number of bacilli in the suspension, and that therefore these areas represented colonies of the bacteriophage and did not result from the lysis of sensitive organisms as others (233, 376, 394) have maintained. D'Herelle (125) summarized his views as follows:

The bacteriophage is an ultra microscopic organism, which is very widely disseminated in nature. It only multiplies in contact with living bacteria. It penetrates into the interior of an organism and forms a colony of 15 to 25 elements in the space of an hour and a half. The organism then bursts, liberating the young ultramicrobes. These utilize for their development the bacteria which they dissolve with the aid of the lytic diastase which they secrete. There is only one species of bacteriophage and this can acquire activity against any organism. Bacteria on the other hand can also acquire resistance to the bacteriophage. Infection and death or immunity and recovery depend upon whether the organism or the bacteriophage triumphs in this battle. The products of the bacteria which have

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been dissolved by the bacteriophage also play an active rôle in stimulating the formation of antibodies. The outcome of an epidemic also depends upon these two forces for the active bacteriophage, the agent of immunity, as well as the bacteria causing the epidemic can spread from one individual to another.

D'Herelle (125) suggested that wholesale protection of the population might be accomplished by introducing a quantity of the bacteriophage into the central supply of drinking water.

2. Kabeshima (127) suggested that the phenomenon depended upon the interaction of a catalyst and a proferment, the former being derived from the host while the latter was present in or produced by the bacterium. He believed that this catalyst was produced by some intestinal gland or by the intestinal leukocytes of dysenteric or typhoid patients as a result of an invasion of pathogenic bacteria, i.e., as a protective measure against infection. This catalyst caused bacteria to produce autolytic ferments. These ferments then acted as catalysts to other bacteria and so on from generation to generation. The fact that this substance would withstand being heated to 70°C., that a very minute quantity of filtrate would dissolve a large number of bacilli in a few hours, that it could be kept at 37°C. for four years without undergoing deterioration, that the bacteriolytic substance was not affected by chemicals which destroy most forms of bacteria, suggested that the lytic principle was a ferment and not a living organism (127). D'Herelle (125), however, protested that spore-bearing and other bacteria could satisfy all of the chemical and thermal conditions which Kabeshima had advanced against the hypothesis that a bacteriophage was a living microbe.

3. Bordet and Ciuca (233) suggested that the ability to produce the lytic substances was acquired by bacteria as a result of contact with some external stimulus such as the leukocytic exudate of the peritoneum of a guinea pig. This external influence possibly represented a defense mechanism on the part of the animal. These bacteria were then able to transmit to their descendants the apitude to form this lytic substance or this apitutude for autolysis.

4. Salimbeni (393) suggested that the d'Herelle phenomenon was probably due to some stage in the history of a pleomorphic organism. He examined in a van Tieghan chamber the changes induced

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in a culture of B. shigae by a bacteriophage. He found in addition to the dysentery bacilli a number of small, round or slightly elongated bodies. These developed into typical myxamoebae which ingested and digested the Shiga bacilli. He suggested the name Myxomyces shigophagus for this myxamoeba. Dumas (391), Pettit (393) and Wollman (422) have reported the presence of myxamoebae in their preparations but d'Herelle (125) could find none in his. Whether all instances of bacteriophagy are due to Myxomyces shigophagus or whether these observers were dealing with preparations contaminated by myxamoebae awaits further study.

5. Kuttner (394) proceeded on the theory that the so-called phenomenon of d'Herelle might be due either to an activation of the natural autolysin present in all bacteria, or to the removal of an autolysin inhibiting substance. Once this natural autolysis was liberated, it could in turn liberate an active autolysin from the next generation of bacteria and so on indefinitely. The fact that the autolysin of old or dead cultures cannot be thus reactivated would seem to invalidate this theory.

Discussion

Although much of the evidence is contradictory and unconfirmed, so that it is impossible to form a definite conclusion in regard to the nature of this lytic agent, yet at present the most probable hypothesis is that the lytic agent is an enzyme. The majority of the data with the marked exception of Salimbeni's (393) observation can best be explained on the basis that the lytic principle is an enzyme. Temperature, chemicals, the reaction of the media and the concentration of bacteriophage and bacteria all have an influence on bacteriophagic processes which is similar to that which they have been demonstrated to have on enzymatic phenomena. The optimum reaction for bacteriophagy corresponds very closely to that of the enzyme trypsin. The fact that cultures of lytic organisms as well as bacteriolytic filtrates will not liquify gelatin, however, suggests that the bacteriolytic principle is not trypsin (395). The addition of trypsin to a dysentery culture will not cause the culture to become lytic. It is possible that the bacteriolytic enzyme may be similar to erepsin for the extracts of intestine and liver that Kuttner (394) found to be lytic probably contained erepsin.

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It is probable that this bacteriolytic enzyme is both extracellular and intracellular. If the growth of irregular sensitive colonies on an agar plate is suspended in saline and the suspension centrifuged at high speed and the supernatant fluid passed through a Mandler filter, the filtrate is lytic. If the sediment of organisms is resuspended in saline and this suspension ground in a rotary agate mortar and then filtered, this filtrate is equally lytic (395). The fact that living bacteria are necessary for the transmission of the lytic agent suggests that the lytic agent is not the result of the disintegration of dying or dead cells, but represents either the metabolic excreta of bacteria or the synthetic product of the medium elaborated by the action of the bacteria.

If it is granted that the bacteriophagic principle is enzymatic there are at least two possibilities as to its origin. First, as a result of the stimulus of intestinal secretions, tissue extracts, leukocytes, etc., the bacteria acquire the ability to produce bacteriolytic enzymes and this property becomes an hereditary one. This hypothesis requires the assumption that entirely new characteristics can arise as the result of an external stimulus and though perhaps possible is not probable. Second, certain of the bacteria in any culture already have this ability to produce bacteriolytic eryzmes even though it is only slightly developed and that as a result of the action of intestinal secretions, tissue extracts, leukocytes etc. the multiplication of these lytic or sensitive organisms is favored. Such an hypothesis would also explain the facts that filtrates of normal stock cultures were slightly lytic and that irregular colonies were occasionally found in subcultures of normal strains. Bail's (438) demonstration that broth in which normal Shiga bacilli were repeatedly grown and then centrifuged out, was bacteriophagic strengthens this hypothesis. The small amount of lytic substance produced by each growth of organisms remained in the broth and after several reinoculations it became sufficiently concentrated to be readily demonstrable.

Furthermore the explanation is comparable to other bacteriologic phenomena. For instance Teague and Morishima (440) demonstrated that cultures of so-called non-xylose fermenting typhoid bacilli contained a certain number of organisms which fermented xylose slowly and that by suitable cultivation, rapidly fermenting subcultures

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could be obtained. Another comparable example is furnished by the increase in virulence of cultures which is produced by animal passage. Growth within the animal probably favors the multiplication of virulent organisms of the culture at the expense of the non-virulent. Gratia (376) has demonstrated that 11 different types could be isolated from the original Bordet strain of B. coli, so that the second hypothesis appears plausible.

The nature of the external influence contained in intestinal secretions, tissue extracts, leukocytes, etc., which favors the development of organisms is unknown. The one factor that is common to all of these stimuli is that they apparently contain a bacteriolytic enzyme similar to, if not identical with that of the lytic organisms.

It would seem that inasmuch as bacteriolytic filtrates may be obtained from so many sources having no relation to the type of organism attacked by the lytic principle that d'Herelle's phenomenon is not an immunological reaction. The fact that Gengou (427) demonstrated that an extract of the leukocytes of normal animals was non-specifically bacteriolytic would seem to invalidate the suggestion of Bordet and Ciuca (233) that the bacteriolytic power of the peritoneal exudate of guinea pigs inoculated with B. coli was evidence of a protective mechanism against bacterial invasion.

Conclusion

According to the data available at present, d'Herelle's phenomenon probably depends upon a bacteriolytic enzyme produced by bacteria. The amount of this enzyme produced by a culture can be increased by external influences such as intestinal secretions, tissue extracts, leukocytes, etc. The action of these external influences is probably to favor the development of lysogenic organisms at the expense of the non-lysogenic. This enzyme not only dissolves organisms but also favors the multiplication of bacteria which produce this enzyme. In this way the bacteriolytic principle is carried from generation to generation. It is highly improbable that this phenomenon represents a defense mechanism on the part of an animal against bacterial invasion.

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IV. EXPERIMENTAL DYSENTERY

Virchow (223) and Rokitansky (224) before the discovery of B. dysenteriae and its toxins attempted to explain the localization of the lesions of dysentery. The tendency of the membranous lesions of the intestine to confine themselves to the caecum and colon led Virchow (223) to assume that these lesions resulted from the action of products of decomposition upon the intestinal mucosa which was *already* the seat of catarrhal inflammation, and that the projecting points, the cecum, rectum and flexures of the colon were the most affected because the faeces remained in contact with these parts the longest. It is still believed by many clinicians that dysentery, especially in children, is preceded by a non-specific intestinal catarrh. Rokitansky (224) compared the action of dysentery to that of caustic acids and suggested that the necrosis was due to a direct chemical change in the tissues caused by an action starting from the surface. Zoller and Clark (416) suggested that the enormous amounts of formic acid produced by Shiga and Flexner dysentery bacilli might play a significant part in causing the digestive disturbances and toxic symptoms in dysentery. Rokitansky believed that dysentery began as a very superficial inflammation of the mucous mucosa, a simple catarrh, although the typical dysenteric lesions were not encountered until the membranous condition had appeared.

After the discovery of B. dysenteriae and its toxins many experiments were performed on animals to explain the mechanism of infection in bacillary dysentery and to discover the reason for the localization of the intestinal and nervous lesions. Practically all of these attempts have been made with either the cultures or the toxins of B. dysenteriae (Shiga). The results, however, are probably equally applicable to infections with B. dysenteriae (Flexner) if the nerve paralyses produced by the Shiga exotoxin (neurotoxin) be disregarded for nerve lesions caused by Flexner infection are rare (442).

Susceptible animals

The rabbit has been the animal generally used for these experiments. If cultures of the Shiga bacillus or its toxins (119) are injected subcutaneously, intravenously or intraperitoneally into a

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rabbit, a fatal diarrhea usually develops. This is in striking contrast to the absence of characteristic reactions to injections of B. dysenteriae in cats, mice and guinea pigs. The resulting anatomical lesions of the intestines and nervous system are more or less identical with those to be described in man (vide infra). Dogs will develop ulceration of the intestines following injections of Shiga toxin (121) but not after feeding with toxins or cultures although they may succumb to diarrhea. A case of naturally acquired Shiga dysentery in a dog has recently been reported (408). Both large and small varieties of monkeys are susceptible to infection with B. dysenteriae (Flexner) for an epidemic of dysentery has been reported (225) among monkeys in a zoo. The infection orginated from an orangoutang, which arrived ill from the East, and spread to chimpanzees, macaques, and rhesus monkeys and finally to the keeper and his wife. B. dysenteriae (Flexner) was isolated from both animal and human stools. Serious epidemics of clinically and pathologically typical bacillary dysentery have been reported (443) among lambs, but dysentery bacilli have not been isolated.

Conradi (117) produced diarrhea, collapse and paralysis followed by death in rabbits by injecting a large dose of a toxin made by allowing a dysentery culture to autolyse. In four rabbits which survived longer than twenty-four hours there was a diphtheritic membrane of the intestine accompanied by ulceration. Vaillard and Dopter (121) by similar methods found that if the rabbits died in eighteen to twenty-four hours following small subcutaneous doses of toxin, the lesions were in the small intestine but with larger doses the lesions were in the large intestine. With injections of a preparation of dysentery bacilli ground under liquid air and extracted with saline, Lüdke (226) reported that the lesions were chiefly in the small intestine and but rarely in the large intestine. Kikuchi (227) injected the peritoneal exudate of guinea pigs who had had injections of dysentery bacilli, into rabbits and noted that paralysis was the main result. The chief discrepancies in experimental results with dysentery toxin may perhaps be due to the failure to distinguish between the endotoxin and exotoxin of the Shiga bacillus.

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Nervous lesions due to exotoxin (neurotoxin)

Dopter (228) made the first comprehensive study of the effect of dysentery toxin on the central nervous system. He found in rabbits after subcutaneous inoculations of twenty-four hour broth cultures of the Shiga bacillus, or of culture filtrates, that serious lesions might occur in any portion of the nervous system although the medulla was most often affected. The gray matter, and almost exclusively the anterior horns, showed chromatolysis of the nerve cells in a varying degree and occasionally areas of necrosis in which the cellular elements and myelin fibers were destroyed so that scarcely a vestige of them was left. At the same time there was an intense hyperemia, and even hemorrhages might invade the tissue. The white matter was intact. In short, the lesion was that of an acute myelitis, often an anterior poliomyelitis and sometimes a polioencephalitis as well. In addition, Olitsky and Kligler (119) described a perivascular infiltration of small round cells either as a single layer about the sheaths or actually in the sheaths of the vessels of the brain and spinal cords of rabbits who had received exotoxin intravenously. Less frequently these round cells were present as a dense heaped up infiltration about the arterioles and capillaries of the central nervous system especially of the medulla and cervical cord and only slightly of the lumbar cord. These authors, working with exotoxin that had been carefully separated from the endotoxin, stated that a sublethal dose injected intravenously in rabbits resulted in the development of paresis or paralysis of the extremities in two to four days. Both anterior and posterior extremities might be affected; the former more frequently. This paralytic or paretic stage might endure for one to three days and might then be followed by complete recovery. Although the animal might be apathetic, have no appetite and lose weight, yet there were no intestinal symptoms. A lethal dose injected intravenously resulted in paralysis and prostration within twenty-four to forty-eight hours. There was considerable loss of weight. Involuntary evacuations of the bowels occurred but were without blood or mucus. There were no intestinal lesions at autopsy. The incubation period depended on the dose.

Ellinger and Adler (229) believe that the principal action of the neurotoxin is on the heat-regulating and vasomotor centers. Ani-

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mals became poikilothermous after injections of exotoxin. If the body temperature fell very low the animals were unable to compensate in any way. With this fall in temperature the respiratory center was injured and this led to the death of the animal.

Intestinal lesions due to endotoxin (enterotoxin)

Olitsky and Kligler (119) with intravenous injections of a sublethal dose of Shiga endotoxin free from exotoxin produced diarrhea, loss of weight and subnormal temperature in rabbits after twenty-four to forty-eight hours. The stools were frequent and mucoid and occasionally blood-tinged. This state, during which no nervous symptoms occurred, endured for two to three days after which gradual recovery took place, or death followed. If a larger but still sublethal, or a lethal dose was injected intravenously, the animal reacted within twenty-four hours with subnormal temperature, considerable loss of weight and prostration. Severe diarrhea resulted, the stools being fluid and containing much mucus and more or less blood. The sensory and motor functions appeared normal. This state lasted for one to three days after which recovery took place or death followed. At autopsy the peritoneum was dull and its blood vessels injected and the peritoneal cavity contained a serous fluid. The small intestines were usually unaffected except that the vessels in the serosa might be injected. Occasionally the ileum was involved in the same extensive way as the large intestine. The walls of the latter were greatly thickened, edematous, injected and showed small discrete hemorrhages. A glairy gelatinous material covered the serous coat. On opening the intestines, the contents were found to consist of blood tinged mucus. The villi were hyperemic, the mucosa was swollen and revealed discrete hemorrhages and small ulcerations. In some instances necrotic areas were seen, and in one instance an area 2.5 cm. wide encircling the cecum was gangrenous. Microscopically, destruction of the glandular elements, as well as a superficial general necrosis was noted. There was a cellular exudation in the submucosa and considerable edema and degeneration of the muscular layers. There were no lesions in the cerebrospinal nervous system. Hence this poison can be regarded as an enterotoxin, in contradistinction to the exotoxin which is a neurotoxin.

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The intestinal lesions were studied by Flexner and Sweet (120) who stated that rabbits were not subject to infection with dysentery bacilli when they were fed by mouth or when the cultures were injected directly into the abdomen. They noted no effect when an autolysate of Shiga cultures, which is largely endotoxin, was fed *per os* or even injected into the duodenum, so it was assumed that dysentery bacilli and their toxins could not produce intestinal lesions in rabbits by mere contact with the mucosa. They believed that although man undoubtedly absorbed dysentery toxin from the intestines where it was produced by the bacilli, yet rabbits had no such power of absorption. Dysentery toxin is destroyed by pepsin and more slowly by trypsin yet this did not explain the absence of intestinal lesions when toxin was fed by mouth. They could produce intestinal lesions only when the dysentery toxin was injected intravenously, subcutaneously or intraperitoneally. These lesions varied in intensity. The coats of the large intestine were greatly thickened by inflammatory edema. The mucosa was yellowish white and thrown into deep folds and corrugations. Occasionally more or less hemorrhage was associated with the edema. In some of the animals the transverse folds of mucous membrane were affected chiefly; they were swollen, the edges were hemorrhagic and a pseudomembrane was scattered over the surface. The hemorrhage in some cases extended into the serous coat. They believed that the character of the histological lesions in the cecum of these rabbits pointed to an action upon the substance and not primarily upon the surface of the intestine.

After dysentery bacilli were injected intravenously, they were found in the bile so these authors cut the bile ducts to prevent the direct action of the bacilli on the intestinal mucosa and after injecting dysentery bacilli found that the intestinal lesions were negligible but the rabbits died of nervous lesions (neurotoxin). This was analogous to the findings in mercurial colitis. When fatal doses of mercury were injected into normal rabbits, the cecum and the first part of the colon were the seat of hemorrhagic necrosis, and diphtheritic and ulcerative lesions, whereas in rabbits with biliary fistulae the changes in the cecum were much less intense. Flexner and Sweet (120) therefore concluded that the intestinal lesions were the result of repeated excretion of bacilli and toxins with the bile and also through

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the intestinal mucosa of the large intestine especially at the cecum and that they were not due to the direct contact of the bacilli and their products with the mucosa.

Besredka (230), however, has recently shown that when B. dysenteriae (Shiga) and its toxins came in contact with the intestinal mucosa an erosion was formed. He fed one series of rabbits with cultures of living dysentery bacilli and another with killed organisms. Intestinal lesions were produced in both series. Dysentery bacilli did not give rise to septicemia when injected intravenously but pure cultures of these organisms were obtained from the bile and intestinal contents from the duodenum to the distal end of the small intestine. The blood, urine and organs remained sterile. The intestinal lesions were the same whether living bacilli, bacilli killed by heat, or endotoxin were injected intravenously, subcutaneously or fed by mouth. The intestinal lesions following intravenous injections of bacilli or toxins were the most severe, those after feeding by mouth the least severe and after subcutaneous injections they were midway. Following subcutaneous inoculations the bacilli at first remained localized and underwent a certain amount of autolysis. The surviving bacilli were then taken up by the circulation and transferred to the mucosa of the small intestine. The severity of the lesions depended upon the directness of the route that the virus traveled from its entrance into the body and its consequent diminution. The general resistance of the animal as well as the size of the dose injected determined whether death or survival would result.

If it is true that intestinal lesions are produced in rabbits by the contact of dysentery bacilli and toxins with the mucous mucosa, the mechanism of infection and the localization of the intestinal lesions in dysentery is very simply explained. These observations of Besredka (230) would seem to substantiate the views of Rokitansky (224) that the initial catarrh of the mucosa in dysentery was due to a direct chemical action starting from the surface, as well as those of Virchow (223) that the transition from the catarrhal to the diphtheritic membrane stage occurred in the cecum and colon because the intestinal contents remained and were in contact with the mucosa at these points the longest time. That Flexner and Sweet (120) did not find intestinal lesions following contact of toxin and mucosa

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might be explained by the smallness of the dose, for Besredka, in one series of rabbits to which a small dose of toxin was fed, failed to find intestinal lesions. The reduction of the severity of the lesions in rabbits with biliary fistulae is explained by the fact that after intravenous inoculations of toxin, this toxin is excreted by the bile and as the bile ducts were cut the toxin could not reach the mucosa. Besredka, Flexner and Sweet all assumed that the intestinal mucosa excreted toxin and bacilli but it would seem possible that the bile is the chief if not the only means for the virus to reach the intestines from the blood. The production of the intestinal lesions could then be explained by the contact of the mucosa and the toxin as it passes downward from the opening of the common bile duct. This would not necessitate the assumption that the lesions of dysentery are produced by the excretion of the toxin through the intestinal mucosa.

Besredka's theory of intestinal immunity

Besredka (230) as a result of his work suggested that the immunity against bacillary dysentery conferred by one attack of the disease or by prophylactic vaccination was due essentially to the sensitization of the intestinal mucosa to dysentery bacilli and that the antibodies of the blood had a small rôle, or none at all, in the protective mechanism. He based this theory on the fact that the feeding of killed dysentery bacilli (heated vaccine) to rabbits produced agglutinins in the blood. Subsequent feeding of large doses of living dysentery bacilli was harmless for these rabbits although fatal for control animals. The serum of the rabbits who have had this prophylactic feeding of killed dysentery bacilli, however, would not protect other rabbits against feedings of live dysentery bacilli. Moreover subsequent feedings of killed dysentery bacilli to these immunized rabbits did not markedly raise the agglutinin titre of the blood. Besredka's (230) explanation was:

> That the preliminary feeding of killed dysentery bacilli produced an erosion of the intestinal mucosa by contact and when this healed the immunity was complete and subsequent feeding of lethal doses of living dysentery bacilli would not produce death, or feedings of killed dysentery bacilli would not increase the antibody titre of the blood for the sensitized intestinal barrier was impassable. The reason that the antibodies of the blood had

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been looked upon as an index of immunity was because previous methods of prophylactic vaccination had been by subcutaneous and intravenous inoculations. These antibodies, however, merely indicated that there had been a systemic reaction to the vaccine. The real immunity, however, depended upon the excretion of the vaccine with the bile into the intestine and the consequent erosion of the mucosa, healing and immunity. By oral vaccination, immunity was produced without this systemic reaction.

Some doubt has been thrown upon this theory by Zingher and Soletsky (441) who were unable to produce immunity in rabbits by giving them B. paratyphosus B. by mouth in accordance with the plan outlined by Besredka (230). Kanai (445) found that the immunity produced in rabbits by the oral administration of Shiga vaccines was inferior to that produced by subcutaneous inoculations.

V. PATHOGENESIS OF BACILLARY DYSENTERY IN MAN

The mechanism of the production of the lesions of human bacillary dysentery is doubtless similar to that described by Besredka (230) in experimental dysentery in rabbits. The dysentery bacilli in practically all instances are taken into the mouth with food or drink and pass directly to the intestines. There is no evidence that dysentery is primarily a septicemia such as is typhoid fever. The organisms can be cultivated at autopsy from the whole length of the colon and even from the small intestine (120) where there may be no pathological lesions but owing to the peristalsis of the small intestine, a prolonged lodgment of bacilli there in any great numbers is prevented and it is not until the cecum and colon are reached that the organisms have an opportunity to multiply appreciably and produce toxins.

The breaking down and autolysis of the bacterial cells (both Flexner and Shiga varieties) liberates an endotoxin. This endotoxin is a local irritant. To it are to be ascribed the great majority of the intestinal lesions. It may doubtless cause hyperemia alone. It may cause a catarrhal, an ulcerative or a pseudomembranous type of inflammation. Not only is the mucosa affected but also the submucosa, the muscularis and in a few cases even the peritoneal covering. There is an exudation of lymph and cells into the intestinal coats. It is the edema of the submucosa that causes most of the thickening of the intestinal wall. This may be double that in health. The mucous

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membrane may be only hyperemic with an excess of mucus or it may have superficial ulcerations upon the summits of the rugae. It may be covered by a false membrane. In long standing cases the ulcerations may be numerous and confined almost entirely to the lymphatic elements of the intestinal wall. Deep ulceration is not very common in children even after the pseudomembranous type of inflammation.

Bacillary dysentery does not always involve the whole length of the colon even in cases proving fatal in the acute stage, but when only a portion of the intestine is attacked that part will be more or less uniformly affected and no extensive and abruptly defined healthy areas will remain within it, as is so commonly the case in advanced amebic dysentery (3). This difference is perhaps due to the different mechanism of infection in these two diseases. In the former, the lesions are probably the result of the direct contact of the mucous membrane with the endotoxin which diffuses uniformly in the area in which it is liberated. Amebae, on the other hand, may attack the intestinal wall singly or in groups and thus leave healthy areas between the erosions.

As a rule the ulcerations of bacillary dysentery are numerous and have clean surfaces, elevated edges and a base formed by the submucosa. In contradistinction to the ulcers of amebic dysentery, the edges of the ulcers of the bacillary variety are not undermined. The borders are irregular, reddened, swollen and infiltrated. The ulcers of bacillary dysentery in adults may be very extensive leading to the separation of large sloughs, or may extend deeply into the coats of the bowel, causing in extreme cases gangrene, (400) perforation (403) and peritonitis or in less serious cases inducing the exudation of much lymph into the peritoneal coat subsequently producing adhesions. Actual suppuration of the intestinal wall never occurs in uncomplicated cases of bacillary dysentery. However, mucous cysts and submucous abscesses of the wall of the large intestine may occur in chronic cases (374). The ulcers heal with the formation of connective tissue leaving a scar in the mucous membrane that is often pigmented. Many bacilli and cocci are found in the inflamed mucous membranes and are especially numerous in the necrotic portions. In the deeper layers the bacilli are found in small numbers, but in

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the glands, between the gland cells and in the glandular stroma they are very numerous. Cocci are not as a rule found in these latter locations. In the submucosa and often in the muscularis the cell infiltration is accompanied by numerous bacilli. Cultures from these regions have shown the presence of B. dysenteriae in pure culture (77).

What part organisms other than dysentery bacilli play in the production of intestinal lesions is hard to say. It is probable that pyogenic cocci—streptococci chiefly (39)—multiply in the necrotic tissue that results from the local irritation of the dysentery endotoxin. Whether they actually attack the intestinal wall it is impossible to state. Doubtless they play an important part in the production of pus which is often present in large amounts in the exudate and stools.

During the early stages of bacillary dysentery, there is a marked febrile reaction. This is probably the result of a systemic reaction to absorbed endotoxin, as well as to the "cleavage products" that may be absorbed from the necrotic intestinal mucous membrane. It would seem justifiable to assume that this absorbed endotoxin is excreted into the intestines again with the bile as Flexner and Sweet (120) and Besredka (230) have shown to be the case with dysentery toxin that has been introduced parenterally in rabbits. The active peristalsis of the small intestine probably prevents the endotoxin from remaining there long enough to produce irritation of the lining of the jejunum. As with the originally ingested bacilli, it is not until the lower ileum and colon are reached that there is sufficient stasis for the excreted endotoxin to produce dysenteric lesions. This absorption of the endotoxin from the colon and its excretion by the bile thus form a vicious circle.

If the lesions of bacillary dysentery were the result of the excretion of this absorbed endotoxin by the intestinal wall as Flexner and Sweet (120) suggested, the distribution of the lesions would be related to the blood supply and they would probably be more numerous at the attachment of the mesentery. This does not appear to be the case.

The Peyer's patches of the ileum are unaffected or only moderately swollen in bacillary dysentery. The solitary lymph nodes in the

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small intestine may be hyperemic and swollen though they are rarely ulcerated, thus contrasting with the frequency of the ulceration of these nodules in the large intestine.

The severity of the damage to the intestines evidently depends upon the virulence and the endotoxin producing properties of the infecting organism. In patients dying of the so-called "terminal dysentery" (3, 138) in whom malnutrition, scurvy, rickets, pneumonia or other disease is more responsible for death than the dysenteric infection, the intestines may merely be hyperemic or have slight ulceration of the lymph follicles of the colon and lower ileum. The length of the illness does not necessarily determine the severity of the lesions for ulceration and membrane formation are not unusual in infants dying of bacillary dysentery of but a few days duration.

The most essential difference between the lesions of typical acute and chronic bacillary dysentery (which is practically confined to adults) is in their extent. In the former, the whole, or nearly the whole, length of the colon and often also the lower part of the ileum are uniformly involved in an acute inflammatory process which may rapidly prove fatal. In the latter, the process is usually limited to the lower half of the colon and the patient survives long enough to allow of more extensive destruction of the mucous membrane of the affected areas, which presents a worm eaten appearance. The character of the lesion differs mainly in that the earlier fibrinous changes in the mucosa have usually disappeared in the chronic stage and only very extensive irregular depressed ulcers are left which usually run into one another with some general thickening of the mucous membrane. In some instances the intestinal wall may be found to be gangrenous along part of its course, (400, 403). In keeping with this long period of intoxication, the wall of the intestine as well as other organs sometimes shows amyloid change (39).

In infections with the Shiga bacillus the *central nervous system* (228) may be the seat of lesions due to the prolonged absorption of exotoxin to which B. dysenteriae (Shiga) gives rise, as a product of its growth, in the intestine. However, as man seldom absorbs as much exotoxin from his intestines as is usually injected experimentally into a rabbit, these lesions are rarely fatal. Consequently there are but few reports of the postmortem examinations of the brains and

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spinal cords of patients who have died of paralysis following Shiga dysentery. The findings that have been published (343) are similar to those seen in experimental Shiga infections in rabbits, and are analogous to those of poliomyelitis and encephalitis.

VI. CLINICAL DATA IN ADULTS

Hippocrates'[1] original statement that dysentery was a condition characterized by the frequent passage of stools containing blood and mucus, accompanied by straining and tenesmus, has not been improved by any later clinical description. A provisional diagnosis of dysentery is justified with that fundamental picture. Not until the advent of laboratory methods could this syndrome be divided into bacillary and amebic dysentery, typhoid, paratyphoid, cholera and food poisoning. The demonstration of the relationship of liver abscesses to amebic dysentery rendered it possible to diagnose many cases of amebic dysentery without stool examinations but not only do mixed amebic and bacillary infections (46, 60, 355) occur but all liver abscesses are not due to amebae (234) so that reliable cultural methods are usually necessary for a final diagnosis.

Typical cases of amebic and bacillary dysentery, typhoid, paratyphoid (394, 206, 235), cholera and food poisoning present characteristic clinical pictures so that when seen side by side they can, as a general rule, be distinguished. However, it must be remembered that even in the presence of an epidemic of any one of these diseases it occasionally is impossible, without laboratory confirmation, to state that an individual case is of the prevailing type. Among a number of cases sent back from the Dardanelles as amebic and bacillary dysentery I have found some due to infection with B. paratyphosus B, although clinically they were indistinguishable from the remainder of the convoy.

Inasmuch as we have effectual specific remedies for amebic and Shiga dysentery (in adults), an accurate laboratory differentiation of these cases of bloody diarrhea is most essential. Clinical appearances alone are not reliable.

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Incubation period

The time from the initial ingestion of the dysentery bacilli until they have become sufficiently numerous to produce enough toxin to cause clinical symptoms may vary from one to eight days. Dysentery bacilli probably multiply rapidly in the intestine but cultures of the stools rarely show viable dysentery bacilli in great numbers. One to ten colonies for each gram of faeces cultured is a high number even in severe cases. This may be due to the great acidity of the stools that occurs in bacillary dysentery (371, 382), or possibly is a result of d'Herelle's phenomenon (125). Great numbers probably die and autolyse in the intestine and thus liberate a large amount of endotoxin. This endotoxin has two effects; one local, due to contact with the intestinal mucosa according to Besredka (230) and the other systemic due to absorption into the blood stream. The length of the incubation period probably depends upon the quantity and the virulence or toxin producing properties of the infection bacilli that were originally ingested. Lemoine (236) reported a case of twenty-four hours' incubation in which infection occurred via the rectum from the use of a chamber containing dysenteric stools although the soiling of the fingers at stool cannot be excluded. In one instance (231) a culture of the Shiga bacillus came in contact with the conjunctiva and dysentery resulted within twenty-four hours. It is well known (232) that bacteria quickly pass from the conjunctiva to the nose and throat. Laboratory infections of twenty-four to forty-eight hours incubation were observed by Flexner (39), Strong (112) and Kruse (34). In an epidemic caused by river water in a Japanese village (46) the incubation period was in most cases from four to five days.

Onset

The prodromal symptoms of general malaise, fever and headache, that are frequently present during the latter part of the incubation period, are probably due to the systemic reaction to the foreign protein of the absorbed endotoxin. The loss of appetite and nausea either may be due to the same cause or are possibly reflex from the local irritation of the intestinal mucosa by the endotoxin. Frequently there are no prodromata and all of the symptoms are attributable to

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the local effect of the endotoxin. The onset is usually characterized by a griping pain in the abdomen and an urgent desire to defecate, resulting in the passage of ordinary formed feces, which temporarily relieves the pain. The pain, however, soon returns, usually in the umbilical region although other locations are frequent, associated with a desire to defecate and the passage of stools which are now of softer consistency and may be streaked with blood. These attacks are repeated at decreasing intervals so that the patient is more or less continuously at stool. Frequently the stools contain nothing but blood and pus. They are usually acid in reaction and Jacoby (371) believes that this is of diagnostic importance. The griping pains in the abdomen are doubtless due to the passage of the intestinal contents over the inflamed mucous membrane. They may become very intense in severe cases and are plainly distinguished from true tenesmus, the bearing down pain experienced in the rectum during and for a time after the actual evacuation of the bowels. Straining and griping are quite constant features. Tenesmus is commonly associated with dysenteric lesions in the rectum, which usually occur early in the disease. Prolapse of the rectum and consequent incontinence of feces may occur in severe cases with marked tenesmus.

In a choleraform type of bacillary dysentery described by Castellani (7), the onset is sudden, with rice water or serous stools; the patient may vomit and usually becomes rapidly worse. Blood may occasionally appear in the stool. The infecting bacilli in these cases are probably exceedingly virulent and rapidly produce a potent toxin so that the maximal effect is noted early.

Many afebrile cases of non-bloody, non-mucous diarrhea of but twenty-four hours' duration have been proved (57, 58) to be due to infection with dysentery bacilli. The so-called epidemic diarrhea is usually mild dysentery (413). These cases may occur during epidemics of typical dysentery and so be diagnosed but frequently they are sporadic and occur during the winter months. The attack may in no way differ from an ordinary attack of diarrhea due to other causes. In the Northern cities of the United States, the majority of the cases occur sporadically and are of this type. Extensive epidemics, even in asylums, and severe cases are the exception. These isolated cases are frequently overlooked unless the bacteriologist as

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well as the clinician diligently searches for them. In one large hospital but eight cases of bacillary dysentery were diagnosed in eight years, yet in one month when repeated stool cultures were done on all patients with diarrhea, two cases of Shiga infection and one of Flexner infection were discovered. It is probably through these sporadic, mild and frequently undiagnosed cases that bacillary dysentery is often spread (117).

The term pseudodysentery that is sometimes applied to these mild cases of dysentery would seem to be not only superfluous but also misleading. They are just as much true dysentery bacteriologically as the more severe types and, if they are not clearly recognized as such, are dangerous from the public health point of view. These mild cases are due in all probability to dysentery bacilli that produce but a small amount of toxin, so that there is only a catarrhal inflammation of the mucous membrane of the intestine without erosion.

Course

As a rule, the *stools* become slimy and bloody on the second or third day and very soon are composed of pure blood and mucus. Later the mucus becomes thick and colorless with less blood and finally there is the mucopurulent stool so characteristic of bacillary dysentery. The stools are usually small. They have a stale, spermic odor and are generally not offensive. In the severe cases, however, they may become exceedingly foul and contain pus. It is possible that this represents a secondary infection by streptococci or other pus producing organisms. Extremely foul stools are an unfavorable sign. Not infrequently the endotoxin may be so destructive that shreds of mucous membrane and occasionally tubular sloughs (39) may be passed by rectum. In early bacillary dysentery the usual number of stools is from six to fifteen per day. It is impossible in most cases to distinguish the amebic and bacillary varieties by the gross appearance of the stools. Microscopic smears of the stools (222) may be of assistance in diagnosis. If there are no amebae and many cells, the infection is probably bacillary (399). There are, however, many large phagocytes that resemble amebae in the stools of patients with bacillary dysentery. Early in the course of bacillary dysentery smears of the mucus contain a fair number of cells most of

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which are epithelial with some mononuclears and polymorphonuclears. Red blood cells are in clumps and scattered throughout the smear. Later in the disease, the cells increase and are predominately polymorphonuclear.

The *urine* diminishes in amount and at times may contain a trace of albumin. Urination may be painful (dysuria) (39) when the rectum is markedly affected by the endotoxin. Thirst is rarely present in mild cases but in severe ones due to the loss of body fluid, it may become marked.

Vomiting is relatively unusual in mild cases. The *tongue* is usually coated with a white fur. *The temperature* in all but the very mildest cases rises to 101° to 104°F. In mild cases the febrile curve may be intermittent throughout but it often assumes a remittent type for the first few days and gradually declines to normal in the morning while still rising to 100° or 102° in the afternoon. There seems to be no relation between the temperature and the severity of the intestinal lesions (55). A slight return of fever after the curve has been normal for a time is almost always accompanied by an exacerbation of the symptoms except in serum treated cases, when the elevation may be due to serum sickness. As convalescence becomes established, the temperature often becomes subnormal. The *pulse* increases in frequency and in the more severe infections becomes very small. In adults, if the patient is to die, the stools become serous, the pulse rapid and irregular, the temperature drops to subnormal, the number of stools may diminish, hiccough appears and death due to exhaustion generally occurs during the second or third week.

If lesions are present in the upper portion of the colon or in the small intestine, various intoxication symptoms appear, such as headache, general malaise, muscular pains, sleeplessness, numbness and stupor. Delirium is rare except as a terminal symptom. The clinical picture may simulate that of typhoid fever. As a matter of fact, in many of these cases, B. typhosus as well as B. dysenteriae has been isolated (237). I have encountered cases of bacillary dysentery in troops that have become secondarily infected with B. paratyphosus B. (68). Under conditions in which trained nurses are scarce, it is relatively simple for these mixed infections to occur (207) and the possibility should always be considered.

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Physical examinations are usually of no diagnostic importance. Extreme emaciation, atrophy of the general muscular tissues, Hippocratic facies and a retracted, scaphoid and tender abdomen are striking features in cases of long duration. On careful palpation, the thickened bowel may at times be felt, but usually the abdomen is too tender to allow such manipulation. The tenderness is especially acute over the course of the colon. The spleen is not enlarged except in very severe cases (344) or unless malaria, typhoid or other diseases coexist (55).

Severe *hemorrhage* from the bowel is less common than in the amebic form, but Rogers (3) reports the fatal loss of blood from a deep ulcer in the upper part of the rectum in chronic bacillary dysentery.

In occasional cases instead of diarrhea, *constipation* may be the predominating symptom for the disease may be limited to the lower bowel, and feces may be accumulating in the higher region of the colon—a condition which may be recognized by distention. Shiga (77) describes an ascending variety of acute dysentery, which, beginning in the rectum, spreads upwards along the large bowel.

Nervous symptoms

The nervous symptoms due to the Shiga exotoxin are not constantly present in all cases of Shiga infections. This may be due to the fact that the effects of the exotoxin are manifest later in the disease than those of endotoxin. The former must be absorbed into the blood and then probably be accumulated in the nervous tissues to produce sufficient lesions to give rise to clinically detectable nervous symptoms. In many severe cases the patient succumbs to the intestinal lesions before the exotoxin has had time to produce lesions in the central nervous system while in many mild cases in which the dysentery bacilli produce toxin in small amounts the patient has time enough to manufacture antiexotoxin to neutralize the exotoxin before it has sufficiently accumulated in the nervous tissues to produce paralysis. *Peripheral neuritis* is the most common condition caused by the exotoxin. It is generally mild and often confined to one nerve (55, 338). Schlesinger's (240) work would indicate that this neuritis is due to the slow effect of absorbed dysentery toxin similarly to

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the nerve lesions in diphtheria, for he reported *polyneuritis* in twenty soldiers after the dysentery bacilli had disappeared from the stools. *Paralysis*, chiefly paraplegia, is occasionally reported (52, 274, 338).

Recovery

Recovery takes place as soon as the body can produce sufficient antiendotoxin to neutralize the endotoxin and thus prevent further destruction of the mucosa. Besredka (230) believes that the protective mechanism does not involve the antibodies of the blood but that the intestinal mucosa itself, after the erosion caused by the endotoxin has healed, becomes sensitized to dysentery bacilli and acts as a barrier against further infection. That may be true, but it would seem impossible to avoid the assumption that an antiendotoxin must be formed by the blood or other antibody forming center, to neutralize the endotoxin and allow the erosion to heal. Bacteriocidal bodies evidently are not essential to recovery for although dysentery bacilli usually disappear from the intestines a few days after the cessation of the acute symptoms yet some patients after recovery from dysentery may harbor these bacilli in their intestines for months and even years without symptoms. Although these carriers have sufficient antiendotoxin to prevent dysentery bacilli causing inflammation and erosion of the intestinal mucosa and although bactericidal bodies are demonstrable in their sera, yet the mere fact of the continued presence of dysentery bacilli in the stools would seem to indicate that bactericidal substances are not essential. However, as persistent carriers of dysentery bacilli are the exception, the bactericidal bodies may be excreted into the intestines of the majority of patients and account for the disappearance of dysentery bacilli from the stools after recovery. These findings are comparable to those of individuals who become chronic carriers of diphtheria bacilli after convalescence from the disease. The part played by d'Herelle's (125) "bacteriophage" or Kabeshima's (127) bacteriolytic ferment, in determining the patient's recovery is impossible to state at present, (vide supra).

The *duration* is four to eight days in light cases and three to six

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weeks in those that are severe. Shiga (46) found an average duration for all cases of 40 days under medicinal treatment and 25 days under serum therapy. During recovery the stools regain their fecal consistency, the number lessens, and the appetite and strength begin to return. *Relapses*, however, are common, due to dietetic errors, exposure and allowing the patient to get up from bed or to resume a general diet (222) too early.

Reinfections, except for relapses (58), are rare in bacillary dysentery. Shiga (77) noted but four cases among 10,000 patients. However, during mixed epidemics, a convalescent from Flexner dysentery may acquire a new infection with Shiga bacillus (57, 69, 138, 140, 202) and vice versa.

Chronicity

Bacillary dysentery in adults has often been divided into two types, the acute and the chronic. The latter is usually, though by no means always, due to infection with B. dysenteriae (Shiga). Sonne (238) states that the Flexner bacillus was found mainly in mild and sporadic cases. Remlinger, (65) however, reported a severe Flexner epidemic in the Argonne. Many physicians report that no clinical difference can be detected between patients infected with Shiga and Flexner bacilli (69, 140). Moreover, the Shiga and Flexner bacillus may often exist in the same patient (57, 69, 138, 140, 202). Inasmuch as the chronic cases begin in a manner similar to those that are acute, this differentiation is not distinct. Chronicity is perhaps better described as a complication of dysentery rather than as a distinct variety.

Although the acute stages insensibly merge into the chronic disease, so that no definite line can be drawn between them, yet for purposes of analysis Rogers, (3) has taken a duration of one month or more to indicate chronicity. As a general rule, bacillary dysentery terminates in either death or recovery within a few weeks, and but comparatively rarely lingers on with longer or shorter remission for several months, as is not uncommonly the case with inadequately treated amebic disease. Some observers (260, 402, 409), however, have reported that 5 per cent of all cases of dysentery become chronic.

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Chronic dysentery in children is extremely rare. The remissions are not so complete and lengthy in the bacillary type as in the amebic variety, the disease tending to run on unchecked until the patient eventually develops some immunity to the infection and slowly recovers, or, worn out by his sufferings, succumbs to exhaustion, inanition, steady loss of body fluid or to some intercurrent infection.

Dysentery carriers

There is no definite division of convalescent dysentery patients, whose stools continue to harbor B. dysenteriae, into chronic cases and persistent carriers. Fletcher and MacKinnon (175) in a recent study of 1782 British soldiers convalescent from dysentery, some of whom gave histories of intermittent dysentery dating from the Boer War, found 74 still excreting dysentery bacilli. The average *Flexner* carrier was in good health, his stools were formed and free from blood and mucus. He was fit to carry on his work unless subjected to very adverse conditions of feeding, temperature or labor which might induce attacks of diarrhoea. The *Shiga* carrier, on the other hand, was generally an invalid, his stools usually contained blood and mucus and he had frequent attacks of diarrhoea. Furthermore, he often became a mental wreck. Cases of this chronic carrier state, lasting from two to ten years, have been noted. Arnheim (187) regarded the Shiga carriers as the more important. Other Germans (73) stated that Flexner carriers were too numerous to quarantine. The number of dysentery carriers found appears to depend on the epidemic and also possibly on the conditions under which the bacteriologist must work. The usual percentage is rarely more than one per cent (151, 186, 239) but one author reported that 13 per cent of his convalescent patients became carriers of the Flexner bacillus (75).

One investigator (186) suggests that B. dysenteriae in chronic carriers may lurk in the bile as is frequently found to be the case with B. typhosus carriers. Brückner (214) in an autopsy on a dysentery carrier who died of an intercurrent infection, found Flexner bacilli in the small bile ducts in the liver. There were no intestinal lesions. Others (213), however, reported that bile had a destructive and restraining influence on B. dysenteriae both in the intestine and in vitro. Hannon (342) has shown that bile salts were inhibitory to the growth of dysentery bacilli.

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Complications

Perforation and gangrene of the colon and *peritonitis* are rare (241, 400, 403) although the abdomen may be sufficiently tender and rigid to simulate these conditions. However, in 108 fatal Civil War cases studied by Woodward (52) perforation occurred in eleven.

The incidence of *liver abscess* and portal pyemia is negligible. Rogers (3) in 45 autopsies in Calcutta did not find a single instance.

Abscesses in other locations are occasionally reported. Shiga (46) noted one in a convalescent in the upper portion of the rectus abdominalis and in a second case in the gluteal region. The ischiorectal fossa may also be the seat of abscesses (7). They are probably due to secondary infections.

Arthritis. Sydenham (24) noted that dysentery was sometimes associated with rheumatic pains. A swelling of one or more of the large joints and inflammation of the tendon sheaths of a very obstinate character have been noted in certain outbreaks (39, 242) and as a sequel to bacillary dysentery during the Boer War (3). Arthritis of the knees and occasionally of other joints was not an infrequent finding in the cases during the Great War (55, 57, 64, 243, 403, 411, 421) both in untreated cases as well as those under serum therapy. Graham (360) stated that the usual time of onset was between the sixth and twenty-third day after the first symptoms of dysentery. There was no relationship between the time of onset of the arthritis and the severity of the dysentery. In severe cases there was considerable rise of temperature which might oscillate for weeks. In mild cases there was very little if any fever. The swelling and pain were usually though not always confined to one joint. It appears to be due to absorption of endotoxin from the bowel and its excretion into the joint cavities as is known to be the case during the absorption of toxins of septic and gonorrheal origin (244). Joint involvement occurs in both Flexner and Shiga infections. This arthritis tends toward recovery, without going on to suppuration, although it may take some months to resolve. Stiffness may continue for a long period but apparently always ends in complete recovery (360). Cultures of the fluid of these joints have with few exceptions (57) been sterile but the presence of agglutinins in these exudates has frequently

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been demonstrated (55, 57), in some cases in higher dilution than in the blood serum of the patient.

Parotitis may occur in severe cases, and also in moderate cases which run a chronic course (46, 421). It is usually bilateral and appears during the third to the fifth week of the disease. Among 436 patients Shiga (46) found only eight instances of parotitis. The dysentery bacillus was never found in the pus and tissues removed. There is probably no connection between parotitis and the dysentery bacillus. It results from a secondary infection by other organisms present in the mouth (77).

Edema and *ascites* are often seen in debilitated patients or during convalescence (245) or during the terminal stages of protracted cases and are frequently combined with general anemic edema. Isenschmid (246) believes that the edema following dysentery, which is usually ascribed to weakness of the heart, is probably of the starvation edema type. Some of the instances of war edema (Kriegsoedema) seen in Germany were probably sequelae to bacillary dysentery (247). Oberndorfer (248) in autopsies on patients dying of war edema found typical lesions of dysentery in the large intestines.

Functional disturbances of the heart have been prominent in some epidemics (249, 250). Simple endocarditis is not infrequent (251) but the malignant form is rare. Myocarditis and pericarditis may occur in severe cases (251, 411).

Appendicitis has been cited (7, 421) as a complication during convalescence from bacillary dysentery. Vives and others (252), however, state that appendicitis is more frequent in amebic than bacillary dysentery.

Beriberi has been noted as a frequent complication in Japan (46) possibly due to the exclusive diet of rice water gruel so frequently prescribed in the East. The prognosis is not good.

Stenosis of the large bowel, more particularly of the sigmoid flexure, proctitis (403) and periproctitis (256), due to cicatricial contraction of the healing ulcers are among the most important though infrequent sequelae of dysentery as Cantlie (257) has emphasized. The symptoms are: constipation of insidious onset (sometimes alternated with attacks of diarrhoea) associated in due course with a sensation of distension in the abdomen, recurrent colic, loss of appetite, nausea

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and vomiting. Stenosis of the intestines is a serious condition and must be energetically treated. A case of almost complete obstruction of the rectum (258) and a fatal case of intestinal obstruction following dysentery have been reported (259).

Suprarenal insufficiency and postmortem lesions of the suprarenal glands almost identical with those due to diphtheria toxin have been found during epidemics of severe Flexner dysentery (65, 69).

Chronic gastritis and *intestinal ulceration* with pain, meteorism, diarrhoea and dyspepsia (260, 353, 409) may follow dysentery. They are probably the result of direct and reflex irritation due to the cicatricial tissue of the original dysenteric ulcers rather than to a continued action of endotoxin. Alexander (261) found achlorhydria and apepsia in some of his patients after recovery from dysentery. Glaessner (361) has also reported a diminution of pepsin. He believes that the prognosis is more unfavorable in cases with a deficiency of pancreatic secretion and that this should be taken into account in treatment.

As *rare complications* (212, 251, 253, 338) of bacillary dysentery there may be pleurisy, thrombosis, acute and chronic nephritis (419), acute conjunctivitis (345, 346), cyclitis, iridocyclitis (360), iritis (411), prostatitis, rectal carcinomata (398), tetany from hemorrhage in the parathyroid glands (254), pyelocystitis (217, 218, 219), urethritis (345), vaginitis (347), meningomyelitis (362), hemorrhagic encephalitis (363), pyemic manifestations such as pylephlebitis, and meningitis (255). The presence of the last was probably a coincidence. Conjunctivitis was noted in a patient with a Shiga infection but as no dysentery bacilli could be isolated from the eyes, it was assumed to be due to Shiga toxin (346). Nolf (55) reported labial and nasal herpes in a large percentage of his cases (Flexner dysentery).

Blood

The blood picture is often of assistance in distinguishing amebic from bacillary dysentery. In the former *white blood cell counts* of from 20,000 to 40,000 are comparatively common (275) while in the latter, although a slight polymorphonuclear leukocytosis is frequent, the count rarely exceeds 15,000. In more severe Flexner infections Nolf (55) found the average number of white cells to be 25,000

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predominately polymorphonuclears, rising to 47,200 in fatal cases. The leucocytosis disappeared as the dehydration decreased. Marcovici reported (410) that 60 per cent of acute cases had a moderate leukopenia, 6 per cent had a slight leukocytosis (up to 10,900 per cmm.) and that in 34 per cent the white blood count was normal. During convalescence the number of leukocytes was normal. In chronic cases there was usually a leukocytosis (up to 9,400) and occasionally an eosinophilia (3 per cent eosinophiles). He concluded that white blood cell counts were of but little assistance in differentiating dysentery from other forms of diarrhoea. Martinez (444) stated that in bacillary dysentery there was a polynucleosis but no increase in eosinophiles while in amebic dysentery there was a slight eosinophilia and there might be a mononucleosis. Helminthiasis induced a polynucleosis with eosinophilia.

Findlay (263) has recently reported the possibility of differentiating amebic and bacillary dysentery in 90 per cent of cases by the iodin reaction and the production of nuclear pseudopodia in the polymorphonuclear leukocytes.

The *red blood cell counts* are at first relatively increased from the drain of fluid by the bowel, but fall below normal if blood persists in the stools.

Differential Diagnosis, summary

A presumptive diagnosis of bacillary dysentery can be made in temperate climates or during epidemics when the patient has had a febrile onset, passes frequent bloody mucous stools and has colic, tenesmus, resistance over the large bowel, palpable thickening of the wall of the colon, and pain on abdominal pressure. It must be remembered that tenesmus is not a constant symptom because in the majority of instances it only exists when the rectum is affected. The presence of pus in the stool is strongly suggestive of bacillary dysentery (399). The diagnosis of the abortive form of dysentery, which often occurs sporadically in the winter, or in the beginning of epidemics, is very difficult. Similarly too, the diagnosis of dysentery simulating typhoid is not easy. Repeated microscopic examinations of the stools for amebae, and other parasites, numerous stool cultures for dysentery and other bacilli and probably of most importance,

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studies of the agglutination reactions of the patient's serum (after the sixth day) with standardized methods should be undertaken in all cases. A cutaneous reaction for dysentery bacilli similar to the Shick test for diphtheria has been introduced (39) but its value has not been proved.

The conditions necessary for a *definite diagnosis* of bacillary dysentery are the isolation of the bacillus from the patient's stools or a positive agglutination reaction of the dysentery bacillus with his serum (after the sixth day) (235, 264).

Attention must be paid to exclude carcinomata, tuberculosis, polypi, syphilis of the rectum (265), hereditary syphilis (266), hemorrhoids, foreign bodies intussusception, mercurial poisoning, malaria (369), and pressure from uterine tumors (267) as causes of the discharge of blood and mucus from the bowel. Amebic dysentery as well as the cases of diarrhoea that may be due to balantidium coli (89, 90), lambia (91), trichomonas (92, 93) ankylostoma, schistosoma, paragonimus (265) chilomastix mesnili (364) or bilharzia (94) must be differentiated etiologically, clinically and anatomically from bacillary dysentery. It must not be forgotten, however, that mixed infections with amoebae or other parasites and dysentery bacilli may occur (46, 60, 355). The following are perhaps the most important points (46, 404) in the *differentiation of amebic and bacillary dysentery:*

1. The onset is usually acute in bacillary dysentery and gradual in amebic.

2. Amebic dysentery usually runs a chronic course.

3. In the amebic form, no dysentery bacilli can be found, except in the mixed infections of both amebic and bacillary dysentery.

4. In amebic dysentery, toxic symptoms such as high fever, general malaise, anorexia, rapid emaciation, or various nervous symptoms, are not usually observed.

5. In bacillary dysentery liver abscess is never present; it is a very frequent complication of amebic dysentery.

6. The diagnostic value of the emetine treatment. The failure of hypodermic injections of emetine to bring about very marked amelioration of dysenteric symptoms within two to three days is usually sufficient to exclude the presence of amebic disease and thus makes it

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so extremely probable that bacillary infection is present as to indicate active treatment against the latter disease (3). However, emetine therapy is not devoid of danger, for deaths have been reported (268) from its toxic effects. This drug should only be given when the presence of amebic dysentery is suspected and not as a routine method of differential diagnosis.

7. The anatomical processes are also different. According to Kartulis (269) and Kruse (34) the edges of the ulcers are peculiarly undermined in amebic dysentery, while in bacillary dysentery this is never the case and the ulcers are situated on the surface of the folds of the mucous membrane.

VII. CLINICAL DATA IN CHILDREN

Infants and young children are much the worst sufferers from bacillary dysentery. When a household becomes infected, the adults may merely have a mild diarrhea often without blood in the stools, lasting twenty-four to forty-eight hours. The children on the other hand usually have a severe bloody diarrhea which is frequently fatal. In other words the same variety of dysentery bacillus may have but slight effect on the intestinal mucosa of an adult, possibly because of his acquired immunity, while in an infant the organisms usually produce marked inflammation with profound pathological changes. It is unfortunate that bloody diarrhea in children has not been more generally recognized as dysentery and that names such as summer diarrhea, infectious diarrhea and ileocolitis have been applied. Bacteriological studies (47, 48, 124, 138, 149, 150, 151, 153, 154, 215, 270) in many cities have repeatedly proven that the great majority, if not all cases, of bloody diarrhea in children are due to B. dysenteriae. Bacillary dysentery in children can be recognized in nearly all instances by the clinical data alone.

The onset is usually sudden, the first symptom being a loss of appetite, feverishness and irritability or drowsiness. Vomiting and convulsions are not infrequent during the first twenty-four hours. Within a few hours of the initial symptoms there is an increase in the number of stools. These are usually watery for the first day. Blood does not usually appear in the faeces until the second day of the disease. Within three or four days the stools consist almost entirely

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of blood and mucus for the endotoxin has, by this time, produced a marked inflammatory reaction. The number of bowel movements ranges from three to thirty per day. After the first twenty-four hours, the individual stools are exceedingly small, perhaps a teaspoonful of mucus and blood passed after much straining.

A clinical diagnosis of bacillary dysentery is justifiable only when the patient has had an acute febrile onset and the passage of mucous and persistently bloody stools. Children who have diarrhea and have blood in their stools (usually bright blood) on only one or two occasions are usually not suffering from dysentery. The agglutination reactions and stool cultures show this. It is true, however, that infants whose stools contain much pus even without blood almost always have dysentery. Smears of the stool stained with methylene blue should be made to distinguish mucus from pus, for differentiation by the naked eye, is frequently exceedingly difficult. The presence of mucus alone in stools is not significant of dysentery.

Children with bacillary dysentery are usually quite ill and greatly prostrated. For the first few hours they are frequently restless and irritable. Later they become drowsy and apathetic. The appetite may entirely disappear. Loss of weight is rapid. If the stools are very loose for the first day or two and if there is a great disinclination to take water as well as food, dehydration may become a marked and important condition. The numerous and often painful bowel movements frequently make rest and sleep impossible without sedatives.

In most non-fatal cases the temperature falls to normal by the fifth to eighth day. The blood gradually disappears from the stools during the second week. The bowel movements become less numerous and assume a fecal character if the appetite improves so that food is taken.

If the child has been suffering from simple diarrhea or some other disease at the time of the infection with bacillary dysentery, the character of the onset is frequently masked. Usually, however, there is a history of a sudden rise in temperature followed by an increased number of stools containing blood and mucus. Mild non-bloody diarrhoea due to B. dysenteriae may occasionally occur in children as well as in adults.

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With most of the cases in well nourished children who die in the early stages of bacillary dysentery as the result of an overwhelming intoxication, a pseudomembranous type of inflammation is found. Doubtless the process in the milder cases is catarrhal in type with or without superficial ulceration. Deep ulceration is found in protracted cases and is especially localized in the lymphoid tissue of the colon and the lower part of the small intestine. This extensive ulceration is common only with poorly nourished children such as are seen in asylum practice.

The leucocyte count is usually slightly increased (48, 200) but is of no diagnostic importance (103).

The physical findings are usually negative. The spleen is rarely palpable. Abdominal tenderness is sometimes present.

Occasionally bronchopneumonia, pyelitis (271), otitis media ulcerative stomatitis (447) and acidosis of the acetone body type (272) may complicate the course of bacillary dysentery in children.

As a general rule the appetite returns when the fever disappears but occasionally there may be persistent refusal to take food so that gavage is necessary for days and even weeks. Three months after recovery from bacillary dysentery, most children have regained their weight. Very few cases become chronic except in asylum practice. Death within the first three weeks or complete recovery is the usual course.

Diagnosis of dysentery in children (summary)

It would seem that in countries where amebic dysentery is not endemic (amebic dysentery is rare among children in the United States (273)), a presumptive diagnosis of bacillary dysentery can safely be made in children who have had a sudden febrile onset and are passing bloody stools. However, as in adults, the laboratory findings are the only absolute criteria. The bacteriological diagnosis of dysentery in children is much simpler than in adults for the intestinal reaction to dysentery bacilli is much more severe in the former and consequently the children's stools consist almost entirely of blood and mucus so that B. dysenteriae is quite readily isolated. In adults the presence of much fecal matter increases the number of B. coli in stool cultures to such an extent that B. dysenteriae is frequently overlooked.

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Fifty to sixty per cent of the cultures of stools of children with dysentery are positive for B. dysenteriae, while in adults the percentage of positive stool cultures ranges from twenty-five to forty. Higher percentages may be obtained if several successive stool cultures are made. *The agglutination reaction of the patient's serum* is the simplest method of laboratory diagnosis and is even more satisfactory than in adults for non-specific agglutinins are rare in the serum of a child even at the low dilution of 1:20; there is less likelihood of the child having had a previous dysenteric infection, from which agglutinins might persist and confuse the diagnosis; the agglutination reaction is frequently positive earlier in the disease in children than it is in adults (occasionally the test may be positive on the second day.)

VIII. PROGNOSIS IN ADULTS AND CHILDREN

In epidemic outbreaks, whether in an institution or in a household, and in infants under one year and in adults over fifty years, the disease is likely to be especially severe, while in the very acute choleraic cases the mortality is also high. With these exceptions, in the great majority of bacillary dysentery cases coming under early observation, especially in Flexner infections, the ultimate *prognosis* is good although convalescence may be tardy. It is far otherwise with neglected patients who have suffered from dysentery from one to several months, often without any treatment, so that extensive ulceration of much of the large bowel is already present on their admission to the hospital. Albu (260) regards complete and permanent recovery from bacillary dysentery as an extremely rare event. Schmidt (402) and Strasburger (409) reported that 5 per cent of their cases of dysentery became chronic. This is a higher percentage than is usually noted. Schmidt stated that the mortality was 40 to 50 per cent among chronic as against 2 per cent in acute cases. In short, chronic bacillary dysentery is a much more difficult disease to deal with satisfactorily (3). The prognosis is poor in mixed infections with B. typhosus and B. dysenteriae especially when typhoid fever is the preceding infection (262). Job and Hirtzmann (369) state that malaria and bacillary dysentery are frequently associated. Owing to the injurious effects of malaria upon the intestines, convalescence from dysentery is apt to be prolonged in malarial subjects.

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Mortality

The *mortality* among adults appears to have diminished during the past two centuries. In one epidemic in Holland in 1729 five thousand people died. The death rate at present varies considerably. Shiga (77) found for the whole of Japan that it was from 22 to 26 per cent. According to Kruse (34) the mortality in Germany is 10 per cent. In a small recent outbreak of Shiga dysentery in Dublin (356) the mortality was about 10 per cent. In Russia (78) and in the British Solomon Islands (404) it ranges from 9 to 18 per cent. Manson (79) reported the mortality from bacillary dysentery among Europeans in India to be from 3 to 22 per cent and among natives from 36 to 40 per cent. At El Tor (80) among the Mecca pilgrims the mortality was 64.4 per cent in 1909. Recent observations by Hotzen (359) in Germany have shown that the dysentery cases in the hot summer of 1917 amounted to 69 per cent of all the cases of acute disturbance of nutrition in infants. Of 123 patients in whom the diagnosis of dysentery was established bacteriologically, 44 per cent succumbed, and, even if only those cases be considered in which diseases other than dysentery could be excluded, the mortality was still 23 per cent. In a series of dysentery cases in American children (48) there were 67 white children with 14 deaths and 4 colored with 1 death, a total mortality of 21 per cent. All of the deaths were in children under 15 months of age. Among 114 cases treated at the Harriet Lane Home for Invalid Children from 1912 to 1918 inclusive, there were 33 deaths, a mortality of 29 per cent.

The reduction of the mortality among troops is very striking. At the siege of Dundalk, Ireland, in 1689 (6), 6000 men among 10,000 dysentery patients died, while in the Great War in spite of many cases there were comparatively few deaths. A quarter of 1 per cent of Nolf's patients (Flexner infections) in the Belgian sector died (55). In a total of 5000 cases, 79 per cent of which were Shiga infections, among the allied troops in Macedonia in the summer of 1918, the mortality was 3.5 per cent (355). Among 1023 cases in three epidemics in German troops on the western front the mortality was 0.4 per cent (433). In one American area in France several hundred mild cases occurred with no deaths. In Salonika the mortality was 1 per cent (58).

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Factors influencing mortality and morbidity

This reduction in mortality may be due to decreased virulence of the organisms, to the absence of famine with which former epidemics were so frequently associated or more probably to better dieting and nursing. With the exception of serum therapy in Shiga infections, the medicinal treatment of dysentery is not sufficiently improved to account for the difference in mortality unless it be that it is now less meddlesome.

Shiga (46) states that the mortality among females is higher than among males. The incidence of bacillary dysentery is greatest among young men from twenty to thirty years of age and children under two years, perhaps because of more frequent exposure, for younger men are not as careful of the origin of their food and drink, while the milk diet of babies, which is an ideal medium for B. dysenteriae, is not as carefully handled as it should be. In infants under one year of age and adults over fifty years the mortality is higher. The majority of the deaths in the dysentery epidemic reported by Csernel (366) were in infants under two years of age and in adults over 70. In the epidemic at Barmen in 1899–1901 (359) the mortality among children was 6.3 per cent as compared with 4.6 per cent among adults. In the recent Dublin epidemic of Shiga dysentery (356) at ages up to forty-five years the mortality was 3.8 per cent and from 45 upwards 43.3 per cent. Kuntze (414) reported that the mortality in nurslings was 41 per cent as contrasted with 20.7 per cent in children over one and a half years. During the occasional epidemics of dysentery that still occur, the mortality is often low in the beginning of the epidemic season (May, June and July) and increases gradually, reaching the maximum in November and December. In winter the mortality is higher, due perhaps to the influence of the season and the chronic course of many of the cases. Rainfall has little influence on the prevalence of dysentery (4). Altitude, however, appears to influence the incidence of the disease. Other things being equal, dysentery decreases as the altitude increases (39).

All races are equally liable to dysentery. Individuals following indoor occupations are less liable to infection than agricultural laborers, soldiers, sailors and explorers (39). Dysentery is notably a poor man's

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disease and a disease of enlisted men rather than of officers. Fatigue, hardship, exposure, starvation and restricted diet are frequently reported as predisposing factors of dysentery.

IX. TREATMENT

There are three fundamental principles in the treatment of bacillary dysentery in adults and children. *First*, to maintain the patient's nutrition and general condition by rest, nursing, diet and the relief of pain so that he may survive long enough to allow his immunity to rise and conquer the disease; *second*, to combat the effects of the disease in the patient by replacing the loss of body with saline; *third*, to kill the causative organism and to neutralize its toxins with specific sera and antitoxins. In addition to these three cardinal procedures, numerous drugs have been recommended to increase the elimination of intestinal contents.

Rest and diet

As soon as a presumptive diagnosis of dysentery has been made, the patient should be sent to bed and kept as quiet as possible. He should not be permitted to get up until the stools are practically normal and the fever has subsided. Rest in bed alone has a marked beneficial influence. Every effort should be made to keep the patient comfortable and free from pain. Morphine, hypodermatically has proven useful if the patient, either adult or child, becomes exhausted from frequent straining and the consequent loss of sleep. Paregoric, however, is the usual preparation of opium given to children. Bismuth has been recommended as a means of coating the inflamed mucosa and relieving griping and tenesmus. It usually fails, however. Bismuth, as roentgenology has proven (277), does not adhere to gastric or duodenal ulcers and leaves filling defects over tuberculous ulcers of the colon (278), so why should it be assumed to cling to dysenteric ulcers? Bismuth subnitrate should never be used for it may produce the serious features of nitrite poisoning. The subcarbonate is harmless. Hot water bottles on the abdomen frequently relieve pain. Application to the anus of ointment containing 4 per cent tannic acid or 5 per cent cocaine or the use of cocaine suppositories has been recommended (276). *Enemata* of warm

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normal saline, starch solution or 4 per cent sodium bicarbonate at the outset have proven useful, especially in children. They not only clean the lower colon but also give the patient relief by reducing the tenesmus.

It is advisable to stop all food and to supply water as long as vomiting persists. Water must be given freely and offered as often as every hour through the febrile stages of the disease (279). Saccharine (1 grain to the quart) may be used for children who persistently refuse plain water. After the first twenty-four or forty-eight hours of the illness, vomiting usually ceases to be a prominent symptom. For *children* under two years, protein milk has been one of the best, if not the best food. This may be given in small amounts even in the first twenty-four hours; 1 ounce every four hours for the first day and then if this is well taken and vomiting does not interfere, it may be increased in amount up to 6 to 7 ounces every four hours according to the age and weight of the child. This food is offered whether or not the patient refuses it. As soon as the diarrhea abates and the child shows definite signs of improvement some carbohydrate may be cautiously added to the protein milk in small amounts (usually by the fourteenth day). In case a child is breast fed, this feeding should be continued but it is usually advisable to give alternate feedings of buttermilk or protein milk, as breast milk alone is too laxative in almost all instances.

The claim that a diet of lactose is beneficial in dysentery is not proved. It has been recommended partly because B. dysenteriae does not ferment lactose and also because a high carbohydrate diet changes the stool flora (171, 172, 173, 337). However, the ingested lactose is broken down into galactose and dextrose long before it reaches the distal third of the ileum and the colon where the dysentery bacilli are harbored. B. dysenteriae will readily ferment dextrose. Whether or not the stool flora is sufficiently changed by a high carbohydrate diet and whether these changes have any marked beneficial effect (171, 172, 173, 321) on the condition of the patient is not at all clear (163).

In older children and adults a milk diet (280) supplemented by broth, eggs and vegetable purees is probably the best.

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The main consideration, as in typhoid fever, is to give as much non-irritating food as possible without producing nausea and diarrhea. The lack of appetite makes feeding extremely difficult and emaciation is frequent. In *children* this anorexia may be so pronounced as to cause death from inanition. It is advisable to wait until the temperature falls to normal before commencing forced feeding. Changing the diet from protein milk to buttermilk or even sweetened whole milk formulae does not appear to influence this lack of appetite. If a child refuses one type of food he usually refuses all food. If the desire for food does not return within one week, however, and the patient becomes very weak from inanition 2 to 6 ounces of water may be given by stomach tube every four hours for the first twenty-four hours. If vomiting does not result, one ounce of protein milk or breast milk is substituted for one ounce of water and the child is gavaged with the mixture. The strength of the mixture is increased, unless the patient vomits, until undiluted protein milk is given. Usually the child will regain his desire for milk given by bottle or cup after a week of gavage feeding. Picard (352) recommends the value of cocoa as a food for children with dysentery.

Injections of normal salt solution

In the more severe cases when the loss of water by the bowel has been extreme and when the patients are markedly dehydrated and cannot retain fluid given by mouth or rectum, sterile normal saline or 5 per cent dextrose should be given *intravenously* in amounts of 125 to 500 cc. according to the size of the patient. Instead of normal saline Von Jaksch (339) recommends the injection of a solution containing sodium chloride 15 parts, calcium chloride 0.45 parts and potassium chloride 0.7 parts in a liter of water. Weinberg, Singer and others (339) inject hypertonic saline. In small children the saline or 5 per cent dextrose may be administered *intraperitoneally* (281). Normal saline is preferable as it is more readily absorbed. This procedure has undoubtedly saved many lives. In many cases repeated injection of saline or dextrose either at twelve or twenty-four hour intervals may be necessary to replace the great loss of body fluid. Subcutaneous injections are painful and do not allow the administration of sufficient fluid. They may be used, however, in children

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if the abdomen is distended. Fluid administered by rectum either by syringe or by a Murphy continuous drip is seldom retained or absorbed by children. However, fluid, either saline, 5 per cent dextrose or boiled tap water, may be given from a continuous drip apparatus into the stomach by a nasal tube fastened in place by adhesive. Stewart (434) has found that in children a drip delivering fifteen drops per minute may be continued four to five days without producing nausea. It may be given continuously or in periods of a half hour alternating with equal periods of rest. In this way 500 to 1000 cc. of fluid may be given daily. If the infant has persistently refused his feedings, protein milk may also be administered through the nasal tube by disconnecting the drip apparatus and substituting a funnel. The prolonged use of a nasal drip is not without danger, however, for fatal erosions of the oesophagus and stomach have occasionally occurred (451).

Specific serum therapy

As B. dysenteriae (Shiga) and (Flexner) are absolutely different culturally and serologically, the success of the serum treatment of bacillary dysentery will depend upon an accurate knowledge of the type of the causative organism in each case and the use of serum containing antibodies for that variety. Polyvalent sera (57, 121, 282, 283, 381) containing antibodies for both Shiga and Flexner varieties are, of course, obtainable and should be used in severe cases until stool cultures or the agglutination reactions of the patient's serum have revealed the type of the infection. However, as the results in Shiga infections have been more favorable than those in Flexner infections, they will be discussed separately.

The therapeutic sera are prepared by the immunization of horses with cultures of Flexner and Shiga bacilli or with the toxins of the Shiga organism. Flexner and Amoss (283) have reported a rapid method for the production of potent antidysenteric serum. Agglutination tests with the dysentery bacillus isolated from the patient's stool and the available therapeutic serum (unless Shiga antitoxin is used) should be made whenever practical (57) to determine whether there are antibodies for this particular strain. Otherwise, serum therapy is often useless. Attempts are now being made (284) to

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standardize Shiga toxins and antitoxins in much the same way as those of the diphtheria bacillus.

a. In Shiga infections

A potent antidysenteric serum should contain antibodies against the exotoxin as well as the endotoxin. Such sera and antitoxins are now obtainable (119, 283). Antitoxin (made by immunizing horses with toxins) is preferable in the treatment of Shiga infections but sera made by the injections of the organisms themselves are also efficacious. Olitsky and Kligler (119) found that a polyvalent antidysenteric serum, although prepared by injecting the cultures alone, contained at least 2000 anti-exotoxic units per cubic centimeter as well as anti-endotoxin and other antibacterial bodies.

Shiga (46) in the Institute for the Research of Infectious Diseases in Tokio has formulated the following rules for the administration of antidysenteric serum or Shiga antitoxin:

1. In mild cases the serum is injected once in a dose of 10 cc.
2. In cases of medium severity the serum is twice injected in doses of 10 cc. The interval is from six to ten hours.
3. In severe cases the largest amounts are injected (40 to 60 cc.) but the daily dose does not exceed 20 cc.

This dosage is very conservative. I have used twice this amount subcutaneously and intramuscularly in children without reactions (285). The doses for adults could be trebled advantageously. The best method of injection is intravenously, care being taken to introduce the serum slowly and to avoid shock. Should a patient give a history of having had asthma, or of being sensitive to horse serum or of having had previous serum treatments, one drop of sterile diluted horse serum (diluted 1:10 with normal saline) should be injected intradermally (401). If the patient has a local or general reaction to this within one hour, 1 cc. of serum should be injected subcutaneously for desensitization. Six to eight hours later the full dose of serum may be given slowly, either subcutaneously or intravenously. If the patient fails to react to the intradermal serum test within one hour, the full dose may be injected at once.

For adults many authorities (286, 287) advise the intravenous injection of 60 to 100 cc. of polyvalent serum as early as possible

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after admission, followed by 40 to 80 cc. subcutaneously or intramuscularly within 12 hours in severe cases. Shiga antitoxin or Flexner serum should be used as soon as the type of infection is known. In children, however, the reactions to intravenous serum are often so severe that injections should be subcutaneous or intramuscular. Serum sickness with fever, urticaria and arthralgia frequently follows serum therapy on about the tenth day (55) both in adults and children but is rarely alarming.

Lantin (288) reports that serum given by rectum is efficacious. If Besredka's (230) theory that the intestinal lesions are due to the contact of dysentery endotoxin with the intestinal mucosa is correct, the administration of antitoxin or antiserum by mouth or rectum in large doses is the most logical method, for it is in the intestine that the endotoxin must be neutralized. Serum given intravenously or subcutaneously must first be excreted into the intestine to counteract the effect of the endotoxin on the intestinal mucosa. Intravenous or subcutaneous serum therapy then in dysentery might be compared to similar procedures in the serum treatment of cerebrospinal meningitis for the administration of specific serum intraspinously in meningitis is obviously the more direct and efficacious method. It may be found that the direct administration of antidysenteric serum by duodenal tube, as Smith (289) suggests, or by rectum (288) or even by appendicostomy or colostomy wounds will reduce the mortality in dysentery more than by the intravenous and subcutaneous routes. Perhaps the efficacy of intravenous and subcutaneous serum therapy in Shiga infections and the apparent lack of benefit from this procedure in Flexner infections may be due to the fact that the Shiga bacillus produces part of its effect by the action on the central nervous system of absorbed circulating exotoxin while the whole picture in Flexner infections is the local action of the endotoxin on the intestinal mucosa.

Under serum therapy in Shiga infections in adults, the disease in its first stages according to Shiga (46) and Flexner (381) is quickly cured or the symptoms markedly ameliorated. In one or two days after the injection, the blood and mucus usually disappear from the stools, pain and tenesmus cease and the patient seems entirely well. On the later use of the serum (at the end of the first week) improve-

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ment of all symptoms is usually noted after a few days. Recovery usually occurs after a week. The effect of the serum upon the fever is very striking; in the majority of cases the temperature may be lowered to normal or even below normal on the next morning after injection. In the ulcerative stage, the action of the serum is not so pronounced as in the earlier stages; nevertheless healing of the ulcers with cicatrization often takes place. Even in the later stages the results are far better than those by any other method of treatment. The mortality in Shiga infections in adults under the use of serum is usually reduced by one-half (54, 78, 117, 243, 290, 291, 292, 390) (from 22 to 26 per cent under medicinal treatment to 9 to 12 per cent (46)). Shiga antitoxin has also been very successful in reducing mortality (78, 118) in adults. In children with Shiga infections, serum and antitoxin, in my limited experience (285), has been rather disappointing. This may perhaps be due to the fact that children often do not respond as well as adults to large subcutaneous and intramuscular injections of horse serum.

b. In Flexner infections

Treatment of Flexner infections with bactericidal and agglutinating sera has been attempted in many epidemics. The therapeutic effects are not nearly as striking as those in Shiga infections and in fact are rather disappointing both in adults (55, 253, 390) and children (138, 200, 285, 293). With large intravenous doses of 40 to 100 cc. of anti-Flexner or polyvalent serum in Flexner infections some authors have noted a reduction in mortality (54, 64, 80 286, 287, 291, 381) but equal benefit is frequently noted with the same amounts of horse serum (73) or normal saline injected intravenously or intraperitoneally. In a few cases of Flexner infection in children which I have treated or seen treated with anti-Flexner serum there has been little or no beneficial result (285). Perhaps the administration of anti-Flexner or polyvalent antidysenteric serum by mouth, duodenal tube or rectum so that it will reach the intestine directly may be of benefit.

Vaccine therapy

Following Shiga's (46) work with vaccines as a prophylactic measure in dysentery epidemics, other observers (55, 253, 310, 311, 405, 415)

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have reported benefit from similar procedures in the treatment of the disease. On the other hand, Rogers and others (312) have had disappointing results with vaccine therapy. As no well controlled experiments have been reported with this method, it is reasonable to suppose that the benefit is more apparent than real as Whittington (313) has proved for the vaccine treatment of typhoid fever. In the treatment of carriers of B. dysenteriae, vaccines have apparently been more successful (7, 55, 175).

Proteosotherapy

Nolf (55, 309) and others (104) have advocated intravenous and subcutaneous injections of 1 per cent Witte's peptone as a valuable therapeutic measure in dysentery. The resulting peptone shock is however occasionally alarming and the dose of the peptone solution must be accurately graded. The injection should be made very carefully and slowly. As a matter of fact, the majority of Nolf's cases were Flexner infections (55) and inasmuch as the mortality with this type is extraordinarily low, "proteosotherapy" should await more confirmation before being widely used.

Drug therapy

Bleeding, purgation, ipecacuanha and occasionally opium were the armamentarium of the past century and a half (10, 11, 12, 25, 30, 52, 294). The first procedure has fallen into disrepute and purgation and ipecac will probably follow. Morphine (420) and paregoric, as has been stated previously, are probably the only drugs at all useful in the treatment of bacillary dysentery.

Cathartics have little to recommend them. Purgation cannot assist the rapidly moving intestine to evacuate its contents and the mucosa has already had sufficient irritation. That castor oil, sodium or magnesium sulphate (295) and calomel (271) at the onset are of value would seem improbable for the infection itself will increase the number of bowel movements before these drugs will have time to produce catharsis. If cathartics and frequent evacuations could rid the intestine of the offending bacteria, all dysentery cases would be of short duration.

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Ipecacuanha (39) has been highly rated as efficacious in the treatment of bacillary dysentery. That it and its active principle emetine are practically specific for amebic dysentery there is no doubt, but the majority of observers deny its benefit in the bacillary variety. In fact many physicians in practice away from laboratories make a diagnosis of bacillary dysentery if ipecac and emetine fail to cause improvement within a few days. One patient with bacillary dysentery treated with benzyl benzoate (372) was apparently benefited. Kohler (412) recommends a German drug mixture called "antidysten." One observer (296) advocates the use of belladonna to counteract the excessive activity of the thyroid and suprarenal glands in dysentery, while another (297) prescribes adrenalin by mouth and rectum to quiet tenesmus. Inasmuch as suprarenal insufficiency has been reported (65) as a complication of dysentery, the adrenalin is perhaps the more logical of these drugs but it is doubtful whether either is really useful.

The ingestion of 300 grams of *kaolin* or *animal charcoal* in oatmeal is advocated as a means of adsorbing dysentery organisms and also rendering the stools more solid (270, 314). Hirsch (315) states that rectal injections of kaolin are more efficacious than the administration by mouth. Weise (316) on the other hand, advises against the use of kaolin on the ground that it forms irritating lumps and does more harm than good. In young children with watery non-dysenteric diarrhea I have found that kaolin and animal charcoal in daily doses of 10 to 20 grams administered in milk will reduce somewhat the number of stools and render them solid by their mechanical action of adsorbing fluid but their beneficial effect has not been particularly apparent.

Irrigation of the colon

In the later stages of the disease and especially in chronic cases, rectal irrigations with tap water (298), 0.01 per cent silver nitrate (79, 299, 300), 0.25 per cent tannin, 0.01 per cent methylene blue (301), permanganate (3), 2.0 per cent sodium salicylate (302) and other solutions (303) have been recommended but their benefit is not striking. Ohly (353) found a 10 per cent ichthyol salve or a 2 per cent silver salt salve useful for local treatment, followed by

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astringents. Schiff (304) reported that rectal injections of 300 cc. of 1 per cent formalin twice a day and continued until the stools were more consistent and then once a day for the next week, were beneficial in Shiga infections. This mode of therapy is painful however. The pain due to repeated introductions of a rectal tube may be largely obviated by the preliminary use of cocaine suppositories, but injections in many cases are not tolerated or retained. In obstinate cases irrigations and flushing of the colon with these solutions through a *colostomy* or *appendicostomy* wound have also been advocated (7, 305, 421) but have not met with enthusiasm (390). Allowing the intestinal contents to drain through a caecostomy wound and thus reducing the irritation of the mucosa of the large intestine has been reported as advantageous (336).

Cooke (306) and others (307) advise touching all chronic ulcers that can be reached through a proctoscope with a solution containing 60 to 120 grains of silver nitrate to the ounce until tenesmus is relieved. The use of sigmoidoscope, however, is occasionally dangerous (446). According to Rogers (3) copper sulphate in a strength of 1 grain to the ounce similarly used is also often of great value and has the advantage of being less painful than silver nitrate. The same author (308) has shown experimentally that silver nitrate in a dilution of 1:10,000, would kill B. dysenteriae in five minutes.

X. MEANS OF SPREAD (EPIDEMIOLOGY)

That dysentery is a communicable disease has been shown, by the review of the numerous epidemics that have occurred among the civilian population and among troops. No one exclusive method of spread or conveyance has been proved but it is probable that, as in typhoid fever, the Oslerian triad (317) of fingers, food and flies is the most important factor.

Graham Smith (318) and others (319, 356, 358, 368, 382, 383) have shown that flies are capable of spreading dysentery. The curves of the case incidence of dysentery among the British troops in Salonika (57) in the A. E. F. (67) and in our series of cases in children (48) demonstrated that the greatest incidence occurred during the summer and autumn months in which flies were the most numerous. B. dysenteriae was isolated from the feet of flies caught in one of the

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Salonika hospitals. After contact with food infected with dysentery bacilli flies could carry and disseminate these organisms for twenty-four hours (320). Bishopp and Laake (388) have reported that flies may frequently travel eight miles from the point of liberation in less than a single day. Paraf (358) made the following observations in a hospital containing patients with bacillary dysentery where flies were very prevalent: (1) Flies swarming round the dejecta of dysentery patients were frequently found to be carriers of the Shiga bacillus. (2) The Shiga bacillus was found in the bodies of flies caught in wards in which dysentery had occurred. (3) The dysentery bacillus was found in food exposed to the air in surgical wards in which there were swarms of flies. (4) As regards the mode of transmission, cultures of flies' legs and wings were positive in only two out of sixteen cases, whereas cultures of the alimentary canal were positive in eleven out of twenty-four cases. (5) The maximum duration of the survival of the dysentery bacillus in the fly's intestine was found to be five days. After that time the cultures were negative.

Through the winter and early spring there are comparatively few cases and in some parts of the country the disease disappears altogether to reappear the next summer. During the flyless months the infecting of food by fingers that have handled the excreta of dysentery patients and contact infections from contaminated clothing and utensils are logical explanations of the spread of dysentery (335). Direct ascending infections from the use of infected latrines (236) and syringes may possibly occur but are surely not frequent. The infection in these cases is probably not ascending but more likely due to the soiling of the fingers.

Carriers of dysentery bacilli have frequently been reported (47, 73, 75, 117, 151, 175, 186, 187, 214, 239, 335, 213). Convalescents may harbor the organisms for many months (46). It is probably by means of these carriers and convalescents that dysentery is carried over from one epidemic season to the other and from one locality to another. Lentz (110) reported the experience with a soldier who, after recovery from dysentery, left his regiment and was the source of a dysentery epidemic in his native village. Other widespread epidemics have similarly been traced to individuals who were convalescent or supposedly cured of dysentery (29, 176, 357, 366).

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Direct contact with a neighbor's child suffering from dysentery or with an adult with a mild diarrhea are responsible for many cases of dysentery in children (48). Two cases of dysentery in newly born infants whose mothers had dysentery have been reported (417). Two or more cases frequently occur in the same house. Small hospital epidemics are not uncommon. The institution of special wards for and the strictest isolation of dysentery patients usually reduces the incidence of infections acquired in hospitals.

Water-born epidemics of dysentery are sometimes reported (57, 322). Dysentery bacilli have occasionally been isolated from the suspected rivers or wells (46) and it has been shown experimentally (176, 322) that these organisms can survive nine days or more in samples of the water (57). Shiga (46) reported one outbreak due to bathing in a stream. It was found that an epidemic of dysentery existed in a village higher up the river and the water had been contaminated by the washing of the infected clothes. Another epidemic in Japan was traceable to the use of a common bath house. An epidemic in Metz in 1870 was restricted to two regiments who derived their water supply from fecally polluted wells (323). The substitution of distilled water in the British Navy (324) and of artesian well water among the Dutch troops in Java reduced the incidence of dysentery nearly to a tenth. Kligler (448) has shown that soil pollution by dysentery is very limited. It probably plays little or no rôle in the spread of the disease.

Amebic dysentery, however, is more likely to be spread by drinking or bathing in infected water while flies are probably the more common method of dissemination of bacillary dysentery during wars (57, 319, 322).

In my experience the infection of the milk and food in the individual households or army messes by flies or attendants' fingers is the probable explanation of its spread. Lorenz (375) in an epidemic of dysentery in an orphanage reported that the milk was probably infected after sterilization by one of the servants who suffered from a dysentery-like condition.

The institution of Baby Welfare Clinics and Feeding Stations in several cities has probably been a great factor in the reduction of dysentery in children, for in the past few years since these have been

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established the number of cases of dysentery in children admitted to hospitals has become steadily smaller. Mothers are taught to keep their infants clean and to give them clean food. Occasionally in epidemics of dysentery among children the milk supply has been suspected (139). I was unable to trace any relationship between any of my cases (48) and the source of the milk supply. The pasteurization of milk and its distribution in bottles instead of being sold in bulk at corner grocery stores have had an important influence in reducing dysentery. This has probably not been because dysentery bacilli in the original milk have been killed by pasteurization, for B. dysenteriae has rarely, if ever, been found in a milk supply, but because the use of pasteurized and bottled milk has educated the public to the necessity of the careful handling of this readily infected food. Knox and Powers (325) were able to reduce the incidence of dysentery among the children whose feedings were supervised by the Babies Milk Fund Association of Baltimore, by insisting that the infants be fed only milk mixtures that have been boiled directly in the feeding bottles (so that the possibility of contaminating the boiled mixture by transferring it to the bottle is obviated). Dysentery is rare in breast fed children (152).

XI. PROPHYLAXIS

When cases occur or are suspected either among adults or children, the patient should be promptly isolated. Those engaged in caring for patients with dysentery should not prepare food for other individuals. The breast feeding of infants should be encouraged. When this is impossible the milk mixtures and the bottles or containers should be boiled. Flies should be suppressed and food and feces rigidly separated. Excreta from patients and all open latrines must be adequately covered or disinfected with lysol, carbolic or other antiseptics. Before a patient is discharged as cured and released from quarantine he should have three negative stool cultures (69) over a period of two weeks. Inasmuch as it is sometimes impossible to detain for long periods ex-soldiers who have chronic dysentery or who are carriers of dysentery bacilli, the British (386) notify the local health officer of the man's home town before discharging any of these patients so that he may enforce precautions. Only by the

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rigid application of these measures can the spread of dysentery be prevented.

The first great step toward the reduction of the incidence of bacillary dysentery in children will be made as soon as it is more generally recognized that the great majority of cases of bloody diarrhea in children are true dysentery. The second step will consist in making this disease both in adults and children reportable to the Health Authorities so that the same measures that have made typhoid fever a comparatively rare disease can be instituted against bacillary dysentery.

Prophylactic vaccination

Inoculation with dysentery vaccines may prove as valuable as is the prophylaxis of typhoid fever particularly for children in cities in which dysentery is prevalent. Heretofore, however, the severe reactions to these vacines have made their general use impractical (222, 230, 326, 327). The immunity conferred probably lasts two to three months (222). Vaccines of the Shiga bacillus are very toxic and frequently give rise to sterile abscesses at the point of inoculation. To avoid this Shiga (46, 241) first used simultaneous injections of vaccine and serum. Various methods of reducing the toxicity of Shiga vaccines have been advocated (328, 366). Busson (329) recommends prophylactic inoculations with dysentery toxin-antitoxin mixtures. Graeme Gibson (330) was able to eliminate the reaction to dysentery vaccine and still establish protection by the injection of a saline suspension of B. dysenteriae (Shiga) and (Flexner) mixed with an equal quantity of absorbed polyvalent antidysenteric serum. The results of this technique are encouraging and further experience may establish its usefulness.

Vincent (349) using an ether killed polyvalent antidysenteric vaccine, containing five Shiga and seven Flexner strains, in doses of 500,000,000 to 750,000,000 bacilli in a series of 2175 men found that during a severe epidemic the incidence of infection was twelve times greater among unvaccinated individuals than among his vaccinated series. The reactions to the injections were very slight. Spolverini (351) recently stated that in a small series of children a vaccine made with various strains of B. coli was useful as a means of curing and preventing enterocolitis.

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Whether or not Besredka's (230) method of administering prophylactic vaccines by mouth will prove effectual in man remains to be seen.

Dysbakta (Boehncke) a German proprietary vaccine (probably a combination of dysentery bacilli, toxin and antitoxin) in spite of earlier favorable reports (328, 331) has recently been shown (332) to have nothing to recommend it. *Lipovaccines* made according to Le Moignac's (333) method have been advocated (334) because of their mild reaction, but the difficulty of insuring their sterility has detracted from their value.

REFERENCES

(1) HIPPOCRATES: Epid. Lib. I, Sect. II and III, 54. De Victus Lib. III, Sect. IV, Aphorisms 24 and 26, Sect. VII, Aphorism 23, etc. (The genuine works of Hippocrates, trans. by F. Adams; publ. by Wm. Wood, N. Y.)

(2) HERODOTUS: 8, 115.

(3) ROGERS, LEONARD: Bacillary dysentery. Dysenteries, their differentiation and treatment. Oxford University Press, 1913, pp. 268–286.

(4) HIRSCH, A.: Handbook of geographical and historical pathology. Trans. from 2d ed., (German) by Creighton, C. New Sydenham Society, London, 1886.

(5) KARTULIS: Dysenterie (Ruhr). In Specialle Pathologie und Therapie (H. Nothnagel). V, Bd. 1, Wien, 1900.

(6) GETTINGS, H. S.: Bacillary dysentery. Trans. Soc. of Trop. Med. and Hyg., London, 1915, viii, 111.

GETTINGS, H. S.: Dysentery, past and present. Jour. of Mental Science, October, 1913.

(7) CASTELLANI, A., AND CHALMERS, A. J.: Bacillary dysentery, Manual of tropical medicine. 3rd ed., Balliere, Tindall and Cox, London, 1919, pp. 1848–1852.

(8) Papyrus Ebers. Trans. by Joachim, Berlin, 1890.

(9) FAYRER: Tropical diseases, London, 1881.

(10) ANNESLEY, JAMES: Researches into the causes, nature and treatment of the more prevalent diseases of India and of warm climates generally, 1828.

(11) TWINING, WM.: Clinical illustrations of the more important diseases of Bengal, 1835.

(12) PARKES, EDMUND A.: Remarks on the dysentery and hepatitis of India, 1846.

McLEOD, A. C.: Acholic diseases, comprising jaundice, diarrhoea, dysentery and cholera in India. London, 1866.

(13) ARETAEUS: De Signis et causis diuturnor morb. Lib. II, cap. IX, ed. Kühn.

(14) CELSUS: De Medicina, lib. IV, cap. 15.

(15) ARCHIGENES, AETIUS: Tetrabibl. III, Sermot. cap. 43.

(16) CAELIUS AURELIANUS: Morbor. chron. lib. IV, cap. VI.

(17) AVICENNA: Canon lib. I, Fen II, Tract II, cap. VII.

(18) GALENUS: De horis affectis lib. II, cap. V and lib. VI, cap. II, ed. Kühn VIII.

(19) FREHER: Rer. Germ. script I, 820.

Digitized by Google

(20) Von Wörd, Frank: Chronik, 1585.
(21) Walsingham: Hist. Angl.
(22) Fennel: Quoted by Fayrer (Tropical diseases, London, 1881); and Hirsch, A. (Lehrbuch d. historisch-geographischen Pathol. Stuttgart, 1881).
(23) Zimmermann: Von der Ruhr in dem Volke. Zürich, 1767.
(24) Sydenham: Works of T. Sydenham, trans. by Latham. London, 1843, vol. i, p. 166 (Syd. Soc. ed. vol. i).
(25) Pringle, John: Observations on the diseases of the army (Flanders). London, 1752, part III, chapt. VI.
(26) Abercrombie, J.: Path. and pract. researches on diseases of the stomach, etc., Edinburgh, 1828, and Philadelphia, 1830.
(27) Hunter, John: Observations on diseases of the army in Jamaica, 1788.
(28) Epidemics of Dysentery at Rioja, Catamarca and Humahuaca, Buenos Aires Corresp. Jour. Amer. Med. Assn., 1919, lxxii, 56, 362, 508.
(29) Editorial:† Outbreak of dysentery in Hayes urban district. Lancet, London, 1919, ii, 621.
Editorial:† Dysentery in London, Med. Press, 1919, ii, 280.
(30) Baly, William: Gulstonian lectures. London Medical Gazette, 1847, xxxix, 441.
(31) MacKinnon, Kenneth: A treatise on the public health, climate, hygiene and prevailing diseases of Bengal and the N. W. Provinces, 1848, p. 306.
(32) Mott, F. W., and Durham, H. E.: Report on colitis or asylum dysentery. (Eng.) May, 1900. Publ. by the asylums committee November 13, 1900.
Mott, F. W.: Colitis or asylum dysentery. Brit. Med. Jour., London, 1901, i, 1050.
(33) Vedder, E. B., and Duval, C. W.: The etiology of acute dysentery in the United States. Jour. Exper. Med., Baltimore, 1902, vi, 181.
(34) Kruse, W.: Neue Untersuchungen über die Ruhr. Deutsche med. Woch., Leipz. u. Berl., 1907, xxxiii, 292: 338.
Kruse, W.: Uber die Ruhr also Volkskrankheit und ihrer Erreger, Deutsch. Med. Woch., 1900, xxvi, 637.
Kruse, W.: Weitere Untersuch. über die Ruhr und die Ruhrbacillen. Ibid, 1901, xxvii, 370 and 386.
Kruse, W., Zur Geschichte des Ruhrforschung und über Variabilität der Bakterien. Ibid., 1903, no. 12.
Kruse, W.: Die Blutserumtherapie bei der Dysenteriae. Ibid, 1903, xxix, 49.
Kruse, W.: Der jetzige Stand der Dysenteriae Frage. Deutsche Aerzte Zeitung, 1902, no. 2.
Kruse, W.: Die Gesundheitsverhältnisse der Aerzte Geistlichen und Oberlehren im Vergleich mit denen anderes Berufe, 1900, xix, 229.
(35) Hehewerth, F. H.: (Utrecht), Über Dysenterie-Bacillen und ihre Einteilung in Grüppen. Centralbl. für Bacteriol., Orig. Bd., Jena, 1916.
(36) Eyre, J. W. H.: Asylum dysentery in relation to B. dysenteriae. Brit. Med. Jour., London, 1904, i, 1002.
(37) Aveline, H. T. S., Boycott, A. E., MacDonald, W. F.: B. dysenteriae (Flexner) in relation to asylum dysentery. Jour. Hyg., Cambridge, Eng., 1908, viii, 309.
(38) Ryder, C. T., Richards, E. T. F., Peabody, A. H., Canavan, M. M., Southard, E. E., and McGaffin, C. G.: Report of an epidemic of bacillary dysentery at the Danvers State Hospital, Massachusetts, in 1908. Boston Med. and Surg. Jour., 1909, clxi, 679–714.

Digitized by Google

(39) DAVIDSON, A., AND FLEXNER, S.: Bacillary Dysentery in System of Med. 2. ed. (Allbutt, T. C., and Rolleston, H. D.). London and N. Y., MacMillan & Co., 1912, vol. II, part II, p. 427–527.

(40) MARSHALL, W. E.: Case of acute sporadic dysentery in a child associated with the presence of B. dysenteriae (Flexner). Jour. Roy. Army Med. Corps., London, 1909, xii, 556.

BAINBRIDGE, F. A., AND DUDFIELD, R.: An outbreak of dysentery. Jour. Hyg., Cambridge, Eng., 1911, xi, 356.

(41) RUSH, BENJAMIN: An inquiry into the cause and cure of "the cholera infantum." Medical Inquiries and Observations, 1777, ii. Philadelphia.

(42) BOOKER, W. D.: The early history of the summer diarrhoea of infants. Arch. of Ped., 1901, xviii, 487.

(43) JACKSON, JAMES: Some remarks on the morbid effects of dentition. New England Med. and Surg. Jour., 1812, i, 12, 113, 329.

(44) HORNER, W. E.: An inquiry into the anatomical characters of infantile follicular inflammation of the gastrointestinal mucous membrane and into its probable idenity with cholera infantum. Amer. Jour. Med. Sc., 1828.

(45) WOODBURY, F.: Significance of bloody discharges from the bowels in young children. Jour. Amer. Med. Assn., 1884, iii, 180.

ADAMS, S. S.: Epidemic dysentery in young children. Am. Jour. Obst., N. Y., 1890, xxiii, 814.

(46) SHIGA, K.: Bacillary dysentery. Mod. Med. 2. ed. (Osler & McCrae), Philadelphia and New York, 1913, i, 766–782.

(47) OHNO: quoted by SHIGA, K.: Mod. Med. 2. ed. (Osler & McCrae), Philadelphia and New York, 1913, i, 770, 771, 776.

(48) DAVISON, W. C.:*†§ Bacillary dysentery in children. Johns Hopkins Hosp. Bull., Baltimore, 1920, xxxi, 225–234.

(49) ASSALINI, P.: Observations on the plague, dysentery and yellow fever or Cadiz, trans. by Neale Adam, New York, 1806.

(50) MONRO: Observations on the means of preserving the health of soldiers. London, 1780.

(51) LYONS: Diseases of the army in the East (Crimea), 1856.

(52) WOODWARD, JOS. J.: Medical and surgical history of the war of the rebellion. Medical, 1880, ii.

(53) OSLER, WILLIAM: The war and typhoid fever. Transactions of the Society of Tropical Medicine and Hygiene, 1914, viii, 45.

(54) ARCHIBALD, HADFIELD, LOGAN AND CAMPBELL: Laboratory report (Gallipoli). Jour. R. A. M. C., 1916, xxvi, 695.

(55) NOLF, P., COLARD, A., DULIERE, A., ROSKAM, J.: Epidemic of bacillary dysentery in 1917 on the Belgian front. Arch. Med. Belges, May, 1918.

(56) MARTIN, G. J., AND WILLIAM, F. E.: Types of dysentery isolated at no. 3 Australian General Hospital, Cairo. Jour. Hyg., Cambridge, England, 1917, xvi, no. 3.

MARTIN, G. J., AND WILLIAM, F. E.: The chance of recovering dysentery bacilli from stools according to time elapsed since onset of disease. Brit. Med. Jour., London, 1918, i, 447.

(57) DUDGEON, L. S., et al:* Studies of bacillary dysentery occurring in the British forces in Macedonia. Med. Research Com. Special Rep. Ser., London, 1919, no. 40.

Digitized by Google

(58) GRAHAM, D.: Some points in the diagnosis and treatment of dysentery occurring in the British Salonika force. Lancet, London, 1918, i, 51–55.

(59) BARTLETT, G. B.: Pathology of dysentery in the Mediterranean expeditionary force, 1915. Quart. Jour. Med., 1917, x, 185.

(60) MCWALTER, J. C.:†* Double dysentery. Med. Press, 1919, ii, 284–6.

(61) WALLER, W. E.:† The use of antidysentery serum in the treatment of bacillary dysentery. A series of 341 consecutive cases treated in Mesopotamia, with tabular account of the incidence of complications. Lancet, London, 1919, ii, 778–80.

(62) BOOKER, W. D.: A bacteriological and anatomical study of the summer diarrhoea of infants. Johns Hopkins Hospital Repts., Baltimore, 1897, vi, 159–258.

BOOKER, W. D.: Case of ulcerative catarrhal dysentery. Tr. Am. Ped. Ass., 1891, iii, 192–200.

(63) DOUGLAS, S. R., COLEBROOK, L., MORGAN, W. PARRY: Report upon a series of cases of dysentery received from Mediterranean expeditionary forces. Med. Res. Com. Sp. Rep. Series London, 1917, No. 6.

MANSON-BAHR, PHILIP: Correlation of the pathology and bacteriology of bacillary dysentery. Jour. R. A. M. C., 1919, xxxiii, 117.

(64) KLEIN, B. G.:*† Serum treatment of bacillary dysentery: Dysentery arthritis, Lancet, London, 1919, ii, 775–8, and Jour. R. A. M. C., 1919, xxxiii, 343.

COWAN, J. N., AND MILLER, H.: Dysentery: "A clinical study." J. R. A. M. C., 1918, xxxi, 277.

LUNN, W. E. C.: Toxemic arthritis as a complication of acute dysentery. J. R. A. M. C., London, 1914, xxii, 310.

(65) REMLINGER, P., AND DUMAS, J.: La Dysenterie de l'Argonne, étude bacteriologique. Ann. de l'Inst. Pasteur, Paris, 1915, xxix, 498.

REMLINGER, P., AND DUMAS, J.: Syndrome capsulaire aigu au cours de la dysenterie bacillaire. Ann. de méd., Paris, 1914–15, ii, 605.

REMLINGER, P.: Compt. rendu de la Soc. de Biol., Paris, 1915, lxxviii, 423 and 433.

REMLINGER, P.: Sur un nouveau bacille dysenterique atypique. Ibid, 1916, lxxix, 576.

(66) TRIBONDEAU, L., AND FICHET, M.: Results de l'analyse bacteriologique des selles dans 217 cas de dysenterie provenant du corps expeditionaire d'Orient (C. E. O.). Bull. Acad. de Méd., Paris, 1916, 3.s. lxxv, 317.

TRIBONDEAU, L., AND FICHET, M.: Note sur les dysenteries des Dardanelles. Ann. de l'Inst. Pasteur, Paris, 1916, xxx, 357.

ARMAND-DELILLE, PAISSEAU AND LEMAIRE: Note sur une epidemie de dysenterie bacillarie à l'armée d'Orient. Bull. et mém. soc. med. d. hôp. de Paris, 1916, 3.s. xl, 1302.

(67) VAUGHN, V. C., JR.: Typhoid fever (and dysentery) in the A. E. F. Jour. Amer. Med. Assn., 1920, lxxiv, 1074.

(68) DAVISON, W. C.: The aerobic flora of dysentery stools in adults and children. Transactions of Society of American Bacteriologists, 21st ann. meeting, Boston, Dec. 31, 1919; Abstracts of Bacteriology, Baltimore, 1920, iv, 15.

(69) RAJCHMAN, L., AND WESTERN, C. T.: Report upon 878 cases of bacillary enteritis. Med. Research. Comm. Special Rep. Ser., London, 1917, No. 5.

(70) WALKO: Wien. klin. Woch., 1915, xxvii, 197 and 236.

(71) SELIGMANN, E., AND COSSMAN: Zur Bakteriologie der Ruhr im Kriege. Münch. Med. Woch., 1915, lxii, 1768.

SELIGMANN, E.: Zur Bakteriologie der Ruhr im Kriege. Ibid, 1916, lxiii, 68.

Digitized by Google

(72) KISSKALT, K.:* Seasonal occurrence of cholera, dysentery, typhoid and typhus. Deutsch Med. Woch., Berlin, 1915, xli, 379.

(73) RUMPEL, T.,* AND SHIGA, G.: Dysentery among the troops. Münchn. Med. Woch., Münich, 1915, lxii, 180, 657, 1021.

SIEBERT, H.: Erfahrungen über die Ruhr bei deutschen Soldaten in der Turkei. Beihefte z. Arch. f. Schiffa- u. Tropenhyg., Leipzig, 1919, xxiii, 97–113.

(74) PALTAUF: Report of meeting of Med. Soc., Vienna, Dec., 1914. Wien. klin. Woch., 1915, xxvii, 44.

LANDSTEINER: Ibid., 485.

STERNBERG: Ibid., 486.

FALTA, W., AND KOHN: Ibid., 583.

(75) VERZAR, F.,* AND WESZECZKY, O.: Carriers of B. dysenteriae (Flexner) (ueber Bazillenträger bei Flexner-Dysenterie). Münch. Med. Woch., 1916, lxiii.

(76) SCHMITZ, K. E. F.: Ueber einen bisher noch nicht bekannten Krankheitserreger aus der Dysenteriegruppe. Ibid., 1918, lxv, 1571.

SCHMITZ, K. E. F.: Ein neuer Typus aus der Gruppe der Ruhrbazillen als Erreger einer grösseren Epidemie. Ztschr. f. Hyg. u. Infectionskrankh., Leipz., 1917, lxxxiv, 449–516.

SCHMITZ, K. E. F.: Centr. f. Bakt., Jena, 1918, lxxxi, 1 abt. Orig. 213.

SCHMITZ, K. E. F.: Neue Mitteilungen über Verwandlungsfähigkeit, Paragglutination unsw. in der Ruhr, Typhus-Coligruppe auf Grund experimentaller Beobachtungen., ibid, 1919, lxxx, 111.

(77) SHIGA, K.: Ueber den Erreger der Dysenterie in Japan. Centr. f. Bakt., Jena, 1898, xxiii, 1te abt, 599.

SHIGA, K.: Ueber den Dysenteriebazillus (B. dysenteriae), ibid, 1898, xxiv, 817, 870 and 913.

SHIGA, K.: Studien über die epidemische Dysenterie in Japan unter besonderer Berucksichtigung der Bacillus dysenteriae. Deutsch. Med. Woch., 1901, Nos. 43, 44, 45 and 48.

SHIGA, K.: Weitere Studien über den Dysenteriebazillus. Ztschr. f. Hyg., 1902, xli.

SHIGA, K.: Die Priorität der Entdeckung des Ruhrbazillus und der Serumtherapie bei der Dysenterie. Deutsch. Med. Woch., 1903, No. 7.

SHIGA, K.: Ueber Versuche zur Schutzimpfung gegen die Ruhr. Deutsch. Med. Woch., 1903, 327.

SHIGA, K.: Observations on the Epidemiology of Dysentery in Japan. Philippine Jour. of Science, 1906, i, 485.

(78) ROSENTHAL, L.: Centr. f. Bakt., 1904, xxxiv, 1te Abt., Ref., 503.

ROSENTHAL, L.: Zur Atiologie der Dysenterie (Moscow). Deutsch. Med. Woch., 1903, xxix, 97.

ROSENTHAL, L.: Ibid., 1904, xxx, 235.

(79) MANSON, P.: Tropical Diseases. 2 ed. (text book), London, 1903.

(80) RUFFER, M. A., AND WILLMORE, J. G.: On the Etiology of Dysentery. Brit. Med. Jour., London, 1909, ii, 862.

RUFFER, M. A., AND WILLMORE, J. G.: The serum treatment of dysentery with notes on the bacteriological diagnosis of dysentery. Brit. Med. Jour., London, 1910, ii, 1519.

CASTELLANI, A.: La Malattia del sonno. Riv. Critica di clinica med., 1903, iv, 652.

CASTELLANI, A.: On the haemolysins produced by certain bacteria. Lancet. London, 1902, i, 440; Some experiments on the precipitins, ibid., 1827.

Digitized by Google

CASTELLANI, A.: Ueber die Verhaltnisse der Agglutinine zu den Schutzkörpern. Zeitschr. f. Hyg., 1901, xxxvii, 381.

CASTELLANI, A.: Some researches on the etiology of dysentery in Ceylon. Jour. Hyg., Cambridge, England, 1904, iv, 495.

CASTELLANI, A., AND CHALMERS, A. J.: Bacillary dysentery in Manual of Tropical Medicine, 2. ed., London and New York, 1913, 1380.

(81) LAMBL: Beobachtung und Studien aus dem Gebiete der Path., Anatomie u. Histologie aus dem Franz-Josef Kinderhospitale in Prag., 1860, p. 365.

(82) CUNNINGHAM, D. D., AND LEWIS: Seventh annual report of the Sanitary Commission with the Government of India; Report on cholera. Calcutta, 1870.

CUNNINGHAM, D. D.: On the development of certain organisms occurring in the intestinal canal. Quart. Jour. of Microscopical Science, 1881, xxi, 234.

(83) LOESCH: Massenhefte Entwickelung von Amebae in Dichdarm. Virchow's Archiv., 1875, lxv, 196.

(84) KARTULIS: Ueber tropische Leberabscesse und ihr Verhältnis zur Dysenterie; Amoeben im Eiter der dysenterischen Leberabscesse und ihre Verhältnisse zur Dysenterie. Cent. f. Bakt., 1887, ii, 745.

KARTULIS: Zur Aetiol. der Dysenterie in Aegypten. Virchow's Archiv., 1886, cv, 521.

KARTULIS: Ueber Reisenamoeben bei chronischen Darmetzündungen der Aegypter. Virchow's Archiv., 1885, xcix, 145.

(85) MASSIOCETINE (MASSIUTIN): 1889, Kiev; Ob. amoebakh kak tchougeiadnykh toslstiah kishok. Wratzch 25, abstracted in Centralblatt für Bakt, vi, 451.

(86) OSLER, WILLIAM: On the amebae coli in dysentery and in dysentery liver abscess. Johns Hopkins Hospital Bull., 1890, i, 53.

OSLER, WILLIAM: Ueber die in Dysenterie und dysenterischen Leberabsess vorhandene amoeba. Centr. f. Bakt., 1890, vii, 736.

(87) COUNCILMAN, W. T., AND LAFLEUR: Amebic dysentery. Johns Hopkins Hospital Repts., 1891, ii, 395.

COUNCILMAN, W. T.: Dysentery. Trans. Ass. Am. Phys., 1892, vii, 113–140.

(88) SCHAUDINN: Untersuch. über die Fortpflanzung einiger Rhizopoden, arb. aus dem Kais. Gesundheitsamte, 1903, xix, Heft 3, 563.

(89) TAGLIAFERRO, J. A.* Balantidium dysentery in Venezuela. Gaceta Med. de Caracas Venezuela, 1918, xxv, 145.

MASON, C. W.:* Case of balantidium coli dysentery. Jour. Parasit., Urbana, Ill., 1919, v, 137.

STEEN, P. H.:* Balantidium colitis. Ugeskrit for Laeger, Copenhagen, 1921, lxxxiii, 662.

DE BELLARD, E. P.:* Balantidium dysentery. Gaceta Med. de Caracas, Venezuela, 1919, xxvi, 27.

(90) SANGIORGI, G.:† Dysenterie in Albania. Pathologica, 1919, xi, 141–4.

(91) FLEMING, R. A.:† Disease in Macedonia. Edinburgh Med. Jour., 1919, i, 215–25.

MANTOVANI, M.:† Lambliosi intestinale. Gazz. d. osp., 1919, xl, 66–9.

LABBE, M.:† La frequence des dysenteries amibiennes meconnues. Bull. Acad. de Méd., 1919, 3.s. lxxxi, 550–552.

LABBE, M.: Les entérites à lamblia intestinal. Presse Méd., Paris, 1919, xxvii 161–162.

Digitized by Google

(92) Besson, A., and Hutchens, H. J.: Practical bacteriology, microbiology and serum therapy. Eng. trans. of 5th French ed., London and New York, Longman & Co., 1913, 362.

(93) Chatterje, G. C.:* Flagellate dysentery. Indian Jour. of Med. Research, Calcutta, 1917, iv, 393.

Rhamy, B. W., and Metts, F. A.: Flagellate protozoa as an etiologic factor of dysenteric diarrhoea, report of a series of cases of trichomonas dysentery including a local epidemic with 17 deaths. Jour. Am. Med. Assn., Chicago, 1916, lxvi, 1190.

Grothusan: Ruhrartige Erkrankungen durch Flagellata. Arch. f. Schiffs- u. Tropen-Hyg., 1920, xxiv, 49.

(94) Low and Castellani, A.: Ibid., 1904, viii.

(95) Basch.: Anatomische und klinische Untersuchungen über dysenterie. Virchow's Archiv, xlv, 204.

(96) Klebs: Die allgemeine Pathologie oder die Lehre von den Ursachen und dem Wesen der Krankheitsprozesse, Jena, 1887.

(97) Chantemesse and Widal: Sur le microbe de la dysenterie, epidemique. Bull. de l'acad. de méd., Paris, 1888, xix, 522.

Chantemesse and Widal: Deutsch. Med. Woch., 1903, xxix, 204.

(98) Grigoriew (Grigorjeff), A. W.: Zur Frage der Mikroorganism bei Dysenterie (Woennomedicinsky Journal, T1, lxxi, 1891, S. 73–102) (Russian) abstracted in Centr. f. Bakt., 1892, xii, Ref. 876.

(99) Ogata: Zur Ätiologie der Dysenterie. Centr. f. Bakt., 1892, xi, 264.

(100) Celli: Etiologia della dissenteria ne' suoi rapporti coli e colle suoe tossine. Annalo d'igien. sperim., 1896, vi, 204.

Celli: Zur Ätiologie der Dysenterie. Internat. Beiträge zur Inneren Medizin, Berlin, Bd. 1.

Celli und Valenti: Nochmal über die Ätiologie der Dysenterie. Central. f. Bakt., 1899, xxv, 481.

Celli und Fiocca: Ueber die Aetiologie der Dysenterie. Centr. f. Bakt., xv–xvii.

(101) Maggiora, A.: Quelques observations microscopic et bacteriologique faites durant une epidemie d'enterocolite dysenterique. Turin, H. Loescher, 1892, repr. from Arch. Ital. de Biol. Turin, 1891–2, xvi.

(102) Arnaud: Recherches sur l'etiologie de la dysenterie aiguë des pays chauds. Ann. de l'Inst. Pasteur, Paris, 1894, 495.

(103) Gilbert, Girod, Lesage and Macaignein, Pfaundler, M., and Schlossmann, A.: The diseases of children. Eng. transl. ed. by H. L. K. Shaw and L. La Fetra, Philadelphia and London., 1908, J. B. Lippincott Co., vol. iii, 295–297.

Rossi, Doria T.: Ueber einige durch das Bacterium coli commune an Kindern hervorgerufene Diarrhöen mit epidemischen Charakter. Centr. f. Bakt., 1892, xii, Orig. 458.

Laveran: Etiologie de la dysenterie. Semaine Med., November 8, 1893.

Finkelstein: Deutsch. Med. Woch., 1896.

Escherich: Ibid., 1898.

Escherich: Verh. d. Kongr. f. innere Medizin, 1899.

Escherich: Zur Aetiologie der Dysenterie. Centr. f. Bakt., 1899, xxvi, Orig. 1 abt., 385.

Digitized by Google

BLOCH, C. E.:* Acute digestive disturbances in infants. Ugeskrift for Laeger, Copenhagen, 1920, lxxxii, 745.

JANOWSKI, W.:* Etiology of dysentery. Paris Médical, Paris, 1921, xi, 152.

(104) FURNO, A.:* Protein therapy in colitis. Rivista Critica di Clinica Medica. Florence, 1920, xxi, 37.

DANYSZ, J.:* Entero antigens in treatment of dysentery. Presse Médicale, 1921, xxix, 362.

(105) CALMETTE: Note sur la presence du bacille pyocyanique dans le sang et l'intestin de dysenteriques en Cochinchine. Arch. de méd. navale, 1892, lx, 207.

(106) LARTIGAN (U.S.A.), ADAMI (Canada): B. pyocyaneus as the cause of dysentery, in Castellani, A., and Chalmers, A. J. Manual of tropical medicine, 3 ed., London, 1919, Bailliere, Tindall & Cox, p. 1841.

(107) LOGAN, W. R.: The intestinal flora of infants and young children. Jour. Path & Bacteriol., Cambridge, 1913–14, xviii, 527–551.

BRAVO AND FRIAS:* Acute colitis in children. Siglo med., Madrid, 1919, lxvi, 1025.

OPPENHEIM, C. J.:* The human fecal streptococci. Jour. Infec. Dis., Chicago, 1920, xxvi, 117–129.

BLACKADER, A. D.:* Epidemic of hemorrhagic diarrhoea due to streptococcus mucosus. Proc. Am. Ped. Soc., June, 1920, Jour. Am. Med. Assn., 1920, 1920, lxxv, 128.

WEISS, H.:* On the etiology of an outbreak of infectious diarrhoea. Arch. Int. Med., Chicago, 1921 ,xxviii, 37–49.

ROSS, S. M., AND PECKAM, C. F.: Enterococcus in certain types of dysentery. Lancet, London, 1920, i, 1362–3.

(108) TSIKLINSKY, MLLE: Contribution à l'etiologie des diarrhees des nourrissons. Ann. de l'Inst. Pasteur, Paris, 1917, xxxi, 517–536.

(109) FLEXNER, S.: On the etiology of tropical dysentery. Philadelphia Medical Journal, 1900, vi, 414.

FLEXNER, S.: On the etiology of tropical dysentery. Centr. f. Bakt., 1900, xxviii, 1te abt, 625.

FLEXNER, S.: A comparative study of dysentery bacilli. Ibid, 1901, xxx, 1te abt, 449.

FLEXNER, S.: A comparative study of dysentery bacilli. Brit. Med. Jour., London, 1901, ii, 786.

FLEXNER, S.: On the etiology of tropical dysentery. Johns Hopkins Hosp. Bull., Baltimore, 1900, xi, 231.

FLEXNER, S., AND BARKER, L. F.: Report of a special commission sent to the Philippines by the Johns Hopkins University to investigate the prevalent diseases of the islands. Johns Hopkins Univ. Circular, 1900, xix, 13.

(110) MARTINI, E., AND LENTZ, O.: Ueber die Differenzerung der Ruhrbacillen mittels der Agglutination. Ztschr. f. Hyg. u. Infectionskrankh., Leipz., 1902, xli, 540.

LENTZ, O.: Vergleich, Cultur, Untersüber die Ruhrbaz. Ibid., 1902, xli, 559.

LENTZ, O.: Dysenterie, in Handbuch d. Mikroörg. (Kolle & Wassermann), 2 aufl, Jena, 1913, iii, 899.

(111) PARK, W. H.: Personal communication.

PARK, W. H., AND DUNHAM: A clinical and bacter. study of a number of outbreaks of disease due to the dysentery bacillus. N. Y. Univ. Bull. of the Med. Sciences, 1902, ii, 187.

Digitized by Google

PARK, W. H., COLLINS AND GOODWIN: The dysentery bacillus group and the varieties which should be included in it. Jour. Med. Res., 1904, xi, 553.

PARK, W. H., AND CAREY: The presence of the Shiga variety of dysentery bacilli in an extensive epidemic of dysentery. Ibid., 1903, ix, 180.

PARK, W. H.: On the interpretation of reactions of agglutination among the bacilli of dysentery. Med. Rec. N. Y., 1903, lxiii, 358.

(112) STRONG, R. P., AND MUSGRAVE, W. E.: Reports on the etiology of the dysenteries of Manila. Report of the Surgeon General of the Army, Washington, D. C., 1900, 251.

STRONG, R. P., AND MUSGRAVE, W. E.: The bacillus of Philippine dysentery. Jour. Am. Med. Assn., Chicago, 1900, xxxv, 498.

STRONG, R. P.: Bacillary dysentery. Therap. Int. Dis., (Forscheimer), New York and London, 1914, v, 253.

(113) HISS, P. H., AND RUSSELL, F. F.: Study of a bacillus resembling the bacillus of Shiga. Med. News, 1903, 289, and Med. Record, New York, 1903, lxiii, 357.

HISS, P. H.: On the fermentation and agglutination characteristics of bacilli of the "Dysentery Group." Jour. Med. Research, 1904–5, xiii, (New Series VIII), 1.

(114) BENIANS, T. H. C.:*†§ Inagglutinable form of Shiga's dysentery bacillus, experimentally derived from an agglutinable culture. Jour. of Path. and Bact., Cambridge (Eng.), 1920, xxiii, 171.

(115) MARSHALL AND KNOX, quoted by DAVIDSON, A., AND FLEXNER, S.: In Syst. of Med. 2 ed., (Allbut, T. C., and Rolleston, H. D.), London, 1912, ii, part II, 493.

(116) NEISSER, M., AND SHIGA, K.: Ueber freie Receptoren von Typhus-u. Dysenteriebazillen und über das Dysenterietoxin. Deutsch. Med. Woch., 1903, xxix, 61.

(117) CONRADI, H.: (a) Ueber eine Kontaktepidemie von Ruhr in der Umgegend von Metz. Festschr. z. 60. Geburtst. v., Robert Koch, Jena, 1903, 551–570.

CONRADI, H.: (b) Ueber lösleiche, durch aseptische Autolyse erhaltene Giftstoffe von Ruhr- und Typhus-bacillen. Deutsch. med. Woch., 1903, xxix, 26.

CONRADI, H.: (c) Veröffilent aus dem Gebiete des Militär-Sanitäts-Wesens, Heft 20.

(118) TODD, C.: On a dysentery toxin and antitoxin. Jour. Hyg., Cambridge, Eng., 1904, iv, 480.

TODD, C.: On a dysentery antitoxin. Brit. Med. Jour., London, 1903, ii, 1456.

(119) OLITSKY, P. K.* AND KLIGLER, I. J.:* Toxins and antitoxins of B. dysenteriae (Shiga). Jour. Exper. Med., 1920, xxxi, 19.

(120) FLEXNER, S., AND SWEET, J. E.: The pathogenesis of experimental colitis in animals and man. Jour. Exper. Med., Baltimore, 1906, viii, 514.

(121) VAILLARD AND DOPTER, C.: Etiologie de la dysenterie epidemique. La Presse Méd., 1903, 375.

VAILLARD AND DOPTER, C.: La dysenterie epidemique. Ann. de l'Inst. Pasteur, Paris, 1903, xvii, 463 and 486.

(122) NEITZ, E. A.:* Nucleoproteids of B. dysenteriae (Shiga). Russky Vrach, Petrograd, 1914, xiii, No. 25.

(123) SONNE, C.:† On the bacteriology of the paradysentery bacilli. Centr. f. Bakt., Jena, 1915, lxxv, 1 abt. orig, 408.

SONNE, C.:† Hypotoxic dysentery bacilli. Kjøbenh., 1914, 230, 8°.

Digitized by Google

(124) TORREY, J. C.: A comparative study of dysentery and dysentery-like organisms. Pt. I, Bacilli producing a typical reaction in litmus milk; Pt. II, Dysentery-like organisms which produce an atypical reaction in litmus milk and should probably be included within the group of pseudodysentery bacilli. Jour. Exper. Med., Baltimore, 1905, vii, 365 and 385.

(125) D'HERELLE, F.:† Sur un microbe invisible antagoniste des bacilles dysenteriques. Compt. rend. Acad. d. sc., Paris, 1917, clxv, 373.

D'HERELLE, F.: On the role of the filterable bacteriophagic microbe in bacillary dysentery. Ibid, 1918, clxvii, 970.

D'HERELLE, F.: On the role of the filterable bacteriophagic microbe in typhoid fever. Ibid., 1919, clxviii, 631.

D'HERELLE, F.: On the role of B. bacteriophagus in avian typhoid. Ibid., 1919, clxix, 932.

D'HERELLE, F.: Mechanism of defense against intestinal bacilli and their etiology. Ibid., 1920, clxx, 72.

D'HERELLE, F.: Le microbe bacteriophage agent d'immunité dans la peste et le barbone. Ibid., 1921, clxxii, 99.

D'HERELLE, F.:† Technique de la recherche du microbe filtrant bacteriophage (Bacterophagum intestinale). Compt. rend. Soc. de biol., Paris, 1918, lxxxi, 1160.

D'HERELLE, F.:†§ Sur le microbe bacteriophage. Ibid., 1919, lxxxii, 1237.

D'HERELLE, F.:† Sur la culture du microbe bacteriophage. Ibid., 1920, lxxxiii, 52.

D'HERELLE, F.:† Sur la resistance des bacteries à l'action du microbe bacteriophage. Ibid., 97.

D'HERELLE, F.: Sur le microbe bacteriophage. Ibid., 247–9.

D'HERELLE, F.:† Sur le microbe bacteriophage. Ibid., 1318–20.

D'HERELLE, F.:† Sur le microbe bacteriophage. Ibid., 1320–22.

D'HERELLE, F.: Sur la nature du bacteriophage. Ibid., 1921, lxxxiv, 339–40.

D'HERELLE, F.: Phenomena coincident with the acquisition of resistance by the bacteria to the action of bacteriophage. Ibid., 384–6.

D'HERELLE, F.: Role of bacteriophage in immunity. Ibid., 538–40.

D'HERELLE, F.: Sur l'historique du bacteriophage. Ibid., 863–4.

D'HERELLE, F.: Sur la nature du bacteriophage. Ibid., 908–9.

D'HERELLE, F.:§ Le microbe bacteriophage. Ibid., 1921, lxxxv, 767–8.

D'HERELLE, F.:* Le bacteriophage—son rôle dans l'immunité. Presse Méd., Paris, 1921, xxix, 463–4.

D'HERELLE, F.:* Le Bacteriophage, Son Rôle dans l'immunité. Masson & Cie, Paris, 1921, 227.

D'HERELLE, F., AND ELIAVA, G.:§ Antibacteriophage serum. Compt. rend. Soc. de biol., Paris, 1921, lxxxiv, 719–21.

D'HERELLE, F.,§ AND ELIAVA, G.:§ Unicité du bactériophage; sur la lysine du bactériophage. Ibid., 1921, lxxxv, 701–2.

FRIEDEMANN, U.: (Review), Ueber das d'Herelle-phänomen. Die Naturwissenschaften, Berlin, 1921, ix, 1010–1014.

AMEUILLE, P.:* (Review), D'Herelle's Bacteriophagum. Annales de Méd., Paris, 1921, ix, 197.

MACHADO, A.,* AND COSTA CRUZ.:* The bacteriophagum, Brazil-Medico, Rio de Janiero, 1921, ii, 347.

Digitized by Google

PUNTONI:* (Review), Ann. d' Ig., 1920, xxx, 643.

EDITORIAL: Do bacteria suffer from infectious diseases? Jour. Amer. Med. Assn., Chicago, 1921, lxxvii, 126–7.

OTTO, R.,* AND MUNTER, H.:* The d'Herelle Phenomenon. Deutsche Med. Woch., Berlin, 1921, xlvii, 1579.

GJORUP, E.:* (Review), Bacteriophagum intestinale. Hospitalstidende, Copenhagen, 1921, lxiv, 214 and 234.

(126) TWORT, F. W.:† An investigation on the nature of ultra-microscopic viruses. Lancet, London, 1915, ii, 1241.

(127) KABESHIMA, T.:† Sur un ferment d'immunité bacteriolysant du mecanisme d'immunite infectieuse intestinale, de la nature du dit "microbe filtrant bacteriophage" de d'Herelle. Compt. rend. Soc. de biol., Paris, 1920, lxxxiii, 219.

KABESHIMA, T.: Sur le ferment d'immunité bacteriolysant. Ibid., 1920, lxxxiii, 471–3.

KABESHIMA, T.: Experimental research on prophylactic vaccination against B. shigae. Compt. rend. Acad. d. sc., Paris, 1919, clxix, 1061.

KABESHIMA, T.:† Therapie experimentale des porteurs de germes. Ibid., 1920, clxx, 71.

(128) BABLET, J.:† Sur la principe bacteriophage de d'Herelle. Compt. rend. Soc. de biol., Paris, 1920, lxxxiii, 1322–24.

(129) METALNIKOW, S.:† B. dysenteriae and d'Herelle's bacteriophage in the larvae of Galleria mellonella. Ibid., 667.

(130) BARBER, M. A.: The variability of certain strains of dysentery as studied by the single-cell method. Philippine Jour. Science, Manila, Sect. B. Trop. Med., 1913, viii, 539.

(131) MURRAY, E. G. D.: An attempt at classification of B. dysenteriae based upon an examination of the agglutinating properties of 53 strains. Jour. R. A. M. C., 1918, xxxi, 257 and 353.

(132) DAVISON, W. C.:*†§ The divisions of the so-called Flexner group of dysentery bacilli. Jour. Exp. Med., Baltimore, 1920, xxxii, 651–663.

(133) DIENES, L.:† Division of the non-toxic dysentery bacilli into 8 groups on the basis of absorption. Zeit. für Immun. u. exp. Ther., 1919, xxviii, i. teil orig., heft 6, 456.

GETTINGS, H. S.,† AND DOUGLAS, S. R.:† An investigation of the Flexner Y group of dysentery bacilli. Med. Res. Com. Special Rep., Series London, 1919, No. 30.

WINSLOW, C. W., KLIGLER, I. J., AND ROTHBERG: Classification of the colon-typhoid group (on fermentation basis). Jour. of Bact., Baltimore, 1919, iv, 429.

ANDREWES, F. W.,† AND INMAN, A. C.:† A study of the serological races of the Flexner group of dysentery bacilli. Med. Res. Comm. Special Rep., Series London, 1919, No. 42.

BERRIDGE, E. M.,† AND GLYNN, E.:† Observations on the classification of forty-eight strains of Flexner-Y and allied bacilli mainly by serological tests. Jour. Path. and Bacteriol., 1920, xxiii, 199.

THJOTTA, J.:†‡ Dysentery in Norway. Med. Rev., Bergen, 1917, xxxiv, 57, 109, 171 and 291.

THJOTTA, J.:*†‡§ On the bacteriology of dysentery in Norway. Jour. Bact., 1919, iv, 355.

Digitized by Google

(134) ANDREWES, F. W.: Dysentery bacilli; the differentation of the true dysentery bacilli from allied species. Lancet, London, 1918, i, 560–563.

(135) MICHEALIS, L.: Ueber kombinierte Eiweiss-Säure-Agglutination insbesondere zur Unterscheidung von Kolik- und Ruhrbazillen. Deutsche Med. Wchnschr., 1915, xli, 244 and 1917, xliii, 1506.

(136) KOPITKO, G. I.,* AND NAGORSKAIA, V. E.:* Etiology and treatment of dysentery. Russky Vract, Petrograd, 1914, xiii, Nos. 15 and 18.

(137) MALLOIZEL AND DATESSEN: Bull. de la Soc. Méd. des Hôp. de Paris, February 8, 1917.

(138) FLEXNER, S., AND HOLT, L. E., EDS.: Bacteriological and clinical studies of the diarrheal diseases of infancy with reference to the Bacillus dysenteriae (Shiga). Stud. Rockefeller Inst. M. Research, New York, 1904, 1–202.

(139) SMILLIE, W. G.: Epidemiology of bacillary dysentery and discussion by Bowditch, H. I. N. York Med. Jour. (etc.), 1916, civ, 1073–1074.

SMILLIE, W. G.:* Epidemiology of bacillary dysentery. Am. Jour. Dis. Child., Chicago, 1917, xiii, 337.

(140) KNOX, J. H. M., AND SCHORER, E. H.: The relation of types of diarrhoea in children to strains of B. dysenteriae. Jour. Exper. Med., 1906, viii, 377.

(141) D'HERELLE, F.:† On an atypical dysentery bacillus. Ann. de l'Inst. Pasteur, 1916, xxx, 145.

ASCOLI: Contribution à la connaissance de la dysenterie de Shiga-Kruse. Bolletino dell instituto Sieroterapico Milanese, March, 1917.

DUMAS, J.:§ Bacterial flora in dysentery cases. Compt. rend. Soc. de biol., Paris, 1919, lxxxii, 1308.

DUMAS, J.: Differential characteristics of bacilli noted in the course of bacillary dysentery. Ibid., 1346.

DUMAS, J.: The avirulence and atoxicity of the bacilli found in the course of bacillary dysentery. Ibid., 1363.

SELIGMAN: Bacteriologie de la dysenterie pendant la guerre. Bull. de l'Inst. Past., May 15, 1917.

GEGENBAUER, V.:† Zur Kenntnis der Ruhr des östlichen Kriegsschauplatzes. Arch. f. Hyg., 1919, lxxxviii, 219.

(142) DUVAL, C. W.: Another member of the dysentery group. Jour. Am. Med. Assn., 1904, xliii, 381.

(143) LEVINE, M.: Dysentery and allied bacilli. Jour. Inf. Dis. Chicago, 1920, xxvii, 31–39.

(144) HIRSCHBRUCH† AND FORTHMANN, M.:† Laboratoriums-Infectionen mit Bakterien der Typhus-Ruhr-Gruppe. Ztschr. f. Med. Beamte, 1919, xxxii, 265–72.

(145) BROUGHTON-ALCOCK:* Two outbreaks of mild dysentery. Brit. Med. Jour. London, 1919, ii, 666.

(146) PETRUSCHKY: Ztschr. f. Hyg. u. Infect.-Krankheiten, 1902, xxxix–xl, 567.

(147) FLETCHER, W.:† Capsulate mucoid forms of paratyphoid and dysentery bacilli. J. Roy. Army Med. Corps., London, 1920, xxxiv, 219.

(148) MAYMONE, B.:† Biological variation of B. shigae observed during an epidemic of bacillary dysentery. Ann. d'ig., 1919, xxix, 653.

(149) HASTINGS, PEASE, SHAW AND JEHLE: In: Pfaundler, M., and Schlossmann, A., The diseases of children. Eng. transl., ed. by H. L. K. Shaw and L. La Fetra, Philadelphia and London, 1908, J. B. Lippincott Co., iii, p. 298.

Digitized by Google

ZAHORSKY, J.: B. dysenteriae in infants. St. Louis Cour. Med., 1902, xxvii.

KENDALL, A. I.: Observations on the etiology of severe summer diarrhoeas of bacterial causation. Boston Med. and Surg. Jour., 1913, clxix, 754–756.

LEINER, K.: Ueber bazillare dysenterie. Speziell im Kindesalter. Wien med. Wchnschr., 1904, xvii, 738–745.

CUERVO, A. H.:* Bacillary dysentery. Rev. med. del Uruguay, Montevideo, 1919, xxii, 117.

PENFOLD, W. J.: Two cases of dysentery in children due to B. dysenteriae of Flexner type. Brit. Med. Jour., London, 1915, ii, 722.

(150) GRAHAM, S. G.:* Bacteriology of infectious diarrhoea. Can. Med. Ass. Jour., Montreal, 1921, xi, 529.

SLAWIK, E.: Serologische und klinische Beitrage zur Kenntnis der Dysenterie der Säuglings. Jahrb. f. Kinderh., Berlin, 1919, n. f., xc, 119–140.

(151) KEUPER, E.:* Dysentery epidemic in young children. Münch. Med. Woch., 1914, lxi, No. 9.

(152) BAUER, J.,* ELLENBECK, FROMME, SIEGEL: Dysentery among young children. Archiv. f. Kinderh., Stuttgart, 1913, lx–lxi (A. Baginsky Festschrift).

(153) WOLLSTEIN, MARTHA: The dysentery bacillus in a series of cases of infantile diarrhoea. Jour. Med. Research, Boston, 1903–4, x, 11–20.

(154) TENBROECK, C., AND NORBURY, F. G.: The presence of B. dysenteriae, B. proteus vulgaris, Bact. welchii, and Morgan's bacillus No. 1, in the stools of cases of infectious diarrhoea. Boston Med. and Surg. Jour., 1915, clxxiii, 280–284.

TENBROECK, C., AND NORBURY, F. G.: B. dysenteriae as a cause of infectious diarrhea in infants. Boston Med. and Surg. Jour., 1916, clxxiv, 785–788.

(155) CHARLTON, G. A., AND JEHLE, L.: On the etiology of bacillary dysentery and of catarrhal enteritis in children. Trans. Assoc. of Am. Physic., Philadelphia, 1904, xix, 405.

(156) DUVAL, C. W., AND SCHORER, E. H.: In Studies from the Rockefeller Inst. for Med. Res., 1904, ii.

(157) MORGAN, H. DE R.: The differentiation of the mannite fermenting group of B. dysenteriae with special reference to strains isolated from various sources in this country. Jour. Hyg., Cambridge, England, 1911, xi, 1.

(158) DAKE, W. J. L.:* Dysenteric bacilli. Mededeel Gen. Laboratorium te Weltevreden, Java, 1919, No. 2–3, p. 68.

(159) KENDALL, A. I., AND SMITH, R. M.: A rapid presumptive test for diarrhea caused by the gas bacillus. Boston Med. and Surg. Jour., 1910, clxiii, 578–579.

KENDALL, A. I., AND SMITH, R. M.: Diarrhea in infants associated with the gas bacillus in the stools. Boston Med. and Surg. Jour., 1911, clxiv, 306–308.

MORSE, J. L.: Infectious diarrhoea. Am. Jour. Med. Sc., Philadelphia, 1915, cxlix, 17–30.

SYLVESTER, P. H., AND HIBBEN, F. H.: The relation of the gas bacillus to infectious diarrhea and other digestive disturbances in childhood. Arch. Pediat., New York, 1915, xxxii, 457–472.

KENDALL, A. I.: The relation of bacteria to the etiology of summer diarrhea in young children. Boston Med. and Surg. Jour., 1915, clxxii, 851–857.

HILL, L. W.: The etiology and treatment of the diarrheal diseases of infancy. Jour. Am. Med. Assn., Chicago, 1919, lxxii, 1653–1658.

Digitized by Google

(160) SIMONDS, J. P.: Classification of the bacillus welchii group of bacteria. Jour. Infect. Dis., Chicago, 1915, xvi, 31–34. Also Stud. Rockefeller Inst. M. Research, New York, 1904, ii, 10.

(161) KNOX, J. H. M., AND FORD, W. W.: Note on the occurrence of Bacterium welchii (Bacillus aerogenes capsulatus) in the dejecta of children. Johns Hopkins Hospital Bull., Baltimore, 1915, xxvi, 27–28.

(162) SISSON, W. R.: A critical review of intestinal bacteriology in relation to certain diarrheas of infants. Boston Med. and Surg. Jour., 1918, clxxviii, 492–498.

(163) DAVISON, W. C.,* AND ROSENTHAL, L. V.:* A bacteriological study of the fecal flora of infants and children. Am. Jour. Dis. Child., Chicago, 1921, xxii, 284–98.

(164) MORGAN, H. DE R., AND LEDINGHAM, J. C. G.: The bacteriology of summer diarrhea. Proc. Roy. Soc. Med., London, 1908–09, ii, Epidemiol. Sect., 133–147.

MORGAN, H. DE R.: Upon the bacteriology of the summer diarrhoea of infants. Brit. Med. Jour., London, 1906, i, 908–912.

MORGAN, H. DE R.: Ibid., 1907, ii, 16.

(165) LEWIS, C. J.: Bacteriology of normal and diarrheal stools of children in Birmingham, England, 1910. Loc. Gov. Board Reports, Med. Suppl., 1910–11, Appendix, B., No. 2, 314.

LEWIS, C. J.: Bacteriology of normal and diarrheal stools of children in Birmingham, England, 1911. Loc. Gov. Board Reports, Med. Suppl., 1911–1912, Appendix B, No. 2, 265.

ORR, T.: Bacteriology of normal and diarrheal stools of children in Shrewsbury, England, 1910. Loc. Gov. Board Reports, Med. Suppl., 1910–1911, Appendix B, No. 5, 374.

ROSS, S. M.: Bacteriology of normal and diarrheal stools of children in Manchester, England, 1910–1911. Loc. Gov. Board Reports, Med. Suppl., 1910–1911, Appendix B, No. 3, 347.

O'BRIEN, R. A.: Bacteriology of normal and diarrheal stools of children in London, England, 1910. Loc. Gov. Board Reports, Med. Suppl., 1910–1911, Appendix B, No. 4, 367.

ALEXANDER, D. M.: Bacteriology of normal and diarrheal stools of children in Liverpool, England, 1911. Local Gov. Board Reports, Med. Suppl., 1911–1912, Appendix B, No. 3, 288.

ALEXANDER, D. M.: Bacteriology of normal and diarrheal stools of children in Liverpool, England, 1912. Loc. Gov. Board Reports, Med. Suppl., 1912–1913, Appendix B, No. 4, 384.

(166) TEJOTTA, T.:*‡ On the bacillus of Morgan No. 1—A Meta—colon-bacillus. Jour. Bact., Baltimore, 1920, v, 67–77.

(167) LEWIS, C. J.: Agglutination reactions of B. Morgan No. 1 and 2 from normal and diarrheal cases. Loc. Gov. Board Reports, Med. Suppl., 1912–1913, Appendix B, No. 3, 375.

(168) KLIGLER, I. J.: The agglutination reactions of the Morgan bacillus No. 1. Jour. Exper. Med., Baltimore, 1919, xxix, 531–536.

(169) GLYNN, E. E.: The relation between bacillus enteritidis sporogenes of Klein and diarrhoea. Thompson Yates Lab. Rep., Liverpool, 1901, iii, 131–150.

(170) FIORE, G.:* Agglutination of Proteus X in various children's diseases. Revista di Clinica Pediatrica, Florence, 1919, xvii, 598.

(171) Bibliography in Tobler "Allgemeine Pathologische Physiologie der Ernährung und des Stoffwechsels im Kindesalter," pp. 236–247.

Digitized by Google

KENDALL, A. I.: Jour. Med. Res., 1911, xxv, 117.
KENDALL, A. I.: Bacteriology, General, Pathological and Intestinal, 1916, p. 579–600.
KENDALL, A. I.: Jour. Biol. Chem., 1909, No. 6, p. 499.
KENDALL, A. I.: Proc. Path. Soc., Philadelphia, 1918, xxxviii, 46.
DISTASO, A.: The change of a normal flora to a typical flora of constipation in vitro. Centr. f. Bakt., 1915, lxxv, Abt. 1, orig. 507.
HERTER: Intestinal Infantilism, 1908.
SCHMIDT: Dit Fäzes der Menschen, 1910, p. 308.
SITTLER: Die Wichtigsten Bakterientypen des Säuglingsdarmes, etc., 1901.
SITTLER: Centr. f. Bakt., 1908, xlvii, p. 14 and 145.
ESCHERICH: Die Darmbakterien des Säuglings, 1886.
MORO: Jahr. f. Kinderh., 1905, lxi, 687 and 870.
DISTASO AND SUGDON: Biochemical Jour., Cambridge, England, 1919, xiii, 153.
(172) TORREY, J. C.: Jour. Infec. Dis., 1915, xvi, 72.
TORREY, J. C.: The regulation of the intestinal flora of dogs through diet. Jour. Med. Res., 1919, xxxix, 415.
(173) PORTER, L., MORRIS, G. B., AND MEYER, K. F.: Certain nutritional disorders of children associated with a putrefactive intestinal flora. Am. Jour. Dis. Child., Chicago, 1919, xviii, 254.
PORTER, L., MORRIS, G. B., AND MEYER, K. F.: The bacteriological analysis of the fecal flora of children. Jour. of Infect. Dis., 1919, xxv, 349.
FIGUEIRA, F., (Rio de Janiero): Extract of bran in infant feeding. Revista di clinica pediatrica, Florence, 1920, xviii, 65.
(174) SCHÜRER, F.:† Ueber die Pathogenese der Dauerausscheider und Bazillenträger. Berl. klin. Wchnschr., 1920, lvii, 106.
(175) FLETCHER, W.,*†§ AND MACKINNON, D. L.:*†§ Contribution to the study of chronicity in dysentery carriers. Med. Res. Com., (England), Spec. Rept., Series 1919, No. 29.
(176) PFUHL.: Vergleich Untersuch uber die Haltbarkkeit der Ruhrbazillen, etc. Zeitschr. f. Hygiene, 1902, xl, 555.
(177) TEAGUE, O., AND CLURMAN, A. W.: Jour. Inf. Dis., 1916, xviii, 601.
TEAGUE, O., AND CLURMAN, A. W.: Jour. Med. Res., 1916, xxxv, 106.
KLIGLER, I. J., AND OLITSKY, P. K.: Method for the isolation and rapid identification of dysentery bacilli. Jour. Am. Med. Assn., Chicago, 1918, lxxi, 2126.
KLIGLER, I. J.: Modification of culture media used in the isolation and differentiation of typhoid, dysentery and allied bacilli. Jour. Exper. Med., Baltimore, 1918, xxviii, 319.
(178) STITT, E. R.: Practical bacteriology, Blood work and animal parasitology, 5 ed., Philadelphia, 1918, p. 38 and 40.
(179) PANGANIBAN, C. S.* AND SCHOBL, O.:* Experience with methylene blue, eosin lactose agar in searching for B. dysenteriae in stools. Philippine Jour. of Sc., Manila, 1919, xiv, 235.
(180) HISS, P. H., AND ZINSSER, H.: Text-book of bacteriology, 3 ed. New York and London, 1916.
(181) RUSSELL, F. F.: The isolation of typhoid bacilli from urine and feces with the description of a new double sugar medium. Jour. Med. Res., 1911–1912, xxv, (new series xx), 217.

Digitized by Google

NICHOLS, H. J.:† The production of CO_2 by the typhoid bacillus and the mechanism of the Russell double sugar tube. Jour. Infect. Dis., 1921, xxix, 82.

(182) ANDRADE, E.: Influence of glycerine in differentiating certain bacteria. Jour. Med. Research, Boston, 1905–1906, xiv (new series ix), 551–556.

(183) CLARK, W. M., AND LUBS, H. A.: A substitute for litmus for use in milk cultures. Jour. Agric. Research, Washington, 1917, x, 105.

(184) GLYNN, E., BERRIDGE, E. M., FOLEY, V., PRICE, M., AND ROBINSON, A. L.: A report upon 2360 enteritis "convalescents" received at Liverpool from various expeditionary forces. Med. Research Comm. Spec. Rep., Ser. London, 1918, No. 7.

(185) FILDES, P.: Report upon recovered cases of intestinal disease in the Royal Naval Hospital, Haslar, 1915–1916. Med. Research Comm. Special Rep., Ser. London, 1917, No. 6.

DE VECCHI, B.,* AND SARTI, C.:* Agglutination of dysentery bacilli by normal and other serums. Annali d'Igiene, Rome, 1918, xxviii, 556.

VALLARDI, C.:† On sero diagnosis in bacillary dysentery. Atti d. Soc. lomb di sc. med. e biol., 1920, ix, 340.

MARTIN, C. J.,* HARTLEY, P.,* AND WILLIAMS, F. E.:* Agglutination in diagnosis of dysentery. Brit. Med. Jour., London, 1918, i, 642.

(186) FLU, P. C.:* Agglutinating Flexner bacilli by normal serum. Mededeel v. d. Burg. Geneesk, Dienst, Batavia, 1918, No. 6 (Eng. ed.), p. 110.

FLU, P. C.:* Flexner bacilli carriers. Ibid., 123.

(187) ARNHEIM: Berl. Klin. Woch., 1915, lii, 1 and 221.

(188) GHON, A., AND ROMAN, B.: Wien. Klin. Woch., 1915, xxviii, 579.

(189) RITCHIE, T. R.: Agglutination of patients' serum in dysentery (normals). Lancet, June 24, 1916.

LOYGUE, G.,* BONNET, H.,* AND PEYRE, E.:* Bacteriologic diagnosis of dysentery. Bull. de la soc. méd. des Hôp., Paris, 1918, xlii, 1096.

MAGNER, W.:* Some observations on dysentery. Lancet, London, 1916, ii, 703.

LEDINGHAM, J. C. G., AND PENFOLD, W. J.: Brit. Med. Jour., London, 1915, ii, 704.

LEDINGHAM, J. C. G., AND PENFOLD, W. J.: Serological tests in dysentery convalescents. Ibid., 1916, i, 47.

HAMBURGER, R.: Untersuchungen über Ruhr. IV. Die Bedeutung der Agglutination für die Ruhrdiagnose. Ztschr. f. klin. Med., Berlin, 1919, lxxxviii, 398–406.

(190) DUHOT, E.,* AND DAMADE, R.:* Serologic tests in dysentery. Jour. de méd. de Bordeaux, 1919, xc, 265.

(191) MCLEOD, J. W., AND RITCHIE, A. G.:† The serum reaction in bacillary dysentery. Observations on agglutination with special reference to the use of freshly prepared bacillary emulsions. Jour. Path. and Bacteriol., Edinburgh and London, 1920, xxiii, 217.

(192) KRUMWIEDE, C.: Personal communication.

(193) DREYER, G.: Discussion on immunity; agglutination. (Proceedings of the British Medical Association, Section of Pathology.) Brit. Med. Jour., London, 1904, ii, 564–567.

DREYER, G.: Widal's reaction with sterilized cultures. Jour. Path. and Bacteriol., Edinburgh and London, 1909, xiii, 331–337.

Digitized by Google

DREYER, G.: On Anvendelse af draebt kultur til Widal-Reakton (The employment of dead cultures for the Widal reaction.) Hosp.-Tid., Kobenh., 1906, 4. R., xiv, 532–542.

DREYER, G.: Discussion on paratyphoid fever. Proc. Roy. Soc. Med., London, 1915–1916, ix, Sect. Med., 9–15.

DREYER, G., AND JEX-BLAKE, A. J.: On the agglutination of bacteria. Jour. Path. and Bacteriol., Edinburgh and London, 1906, xi, 1–28.

DREYER, G., AND WALKER, E. W. A.: On observations on the production of immune substances. Ibid., 1909, xiv, 28–38.

DREYER, G., AND WALKER, E. W. A.: The diagnosis of the enteric fevers in inoculated individuals by the agglutinin reaction. Lancet, London, 1916, ii, 419–423.

DREYER, G., WALKER, E. W. A., AND GIBSON, A. G.: Typhoid and paratyphoid infection in relation to antityphoid inoculation, together with remarks on the importance of the use of prophylactic paratyphoid inoculation. Ibid., 1915, i, 324–328.

DREYER, G., WALKER, E. W. A., AND GIBSON, A. G.: Further remarks on agglutination tests in inoculated persons, and the influence of febrile conditions on inoculation agglutinins. Ibid., 1916, i, 766–768.

DREYER, G., AND TORRENS, J. A.: Paratyphoid (Correspondence). Ibid., 1915, ii, 1369–1370.

DREYER, G., AND INMAN, A. C.: The agglutination curve and its importance in the diagnosis of typhoid and paratyphoid fevers in inoculated persons. Ibid., 1917, i, 365–369.

(194) DAVISON, W. C.: The diagnosis of enteric fever (typhoid and paratyphoid A and B) by agglutination tests. Jour. Am. Med. Assn., Chicago, 1916, lxvi, 1297–1300.

DAVISON, W. C.: Report on prophylactic vaccination with B. typhosus, B. paratyphosus A, and B. paratyphosus B. Jour. Lab. and Clin. Med., St. Louis, 1916–1917, ii, 607–617.

(195) DAVISON, W. C.: The superiority of inoculations with mixed triple vaccine (B. typhosus, B. paratyphosus A, and B. paratyphosus B). Arch. Int. Med., Chicago, 1918, xxi, 437–509.

(196) LEISHMAN, W.: Discussion on paratyphoid fever. Proc. Roy. Soc. Med., London, 1915–1916, ix, Med. Sect., 17–21.

STRONG, R. P., ed.: Trench fever. Report of Commission, Medical Research Committee, American Red Cross, Oxford, 1918. Oxford Univ. Press, p. 40.

(197) KUTSCHER: Munch. Med. Woch., 1915, lxxii, 1, 198 and 213.

(198) ROMM AND BALASHOFF: Centr. f. Bakt., 1912, lxvi, Orig. 246 and 426.

(199) RAVAUT, P.: A propos du sero-diagnostic bacillaire. Bull. méd. de la soc. méd. des hôp. de Paris, 1916, xxxii, 1920.

(200) KNOX, J. H. M., JR.: A contribution to the study of summer diarrheas of infancy. Jour. Am. Med. Assn., Chicago, 1903, xli, 173–179.

(201) LANCELIN, R., AND RIDEAU, I.: Recherches epidemiologiques, bacteriologiques et anatomo-pathologiques au cours d'une epidemie de dysenterie bacillaire observée à Brest en 1916. Arch. de méd. et pharm. nav., Paris, 1917, civ, 360 and 1918, cv, 47.

SPEARES, J., AND DEBONO, P. P.: Agglutination in bacillary dysentery. Jour. R. A. M. C., London, 1919, xxxii, 430–440.

Digitized by Google

SONNE, C.:† The diagnostic value of agglutination of the paradysentery bacilli by the patient's serum. Centr. f. Bakt., Jena, 1915, lxxvi, 1 abt., orig. 65.

(202) GAY, F. P., AND DUVAL, C. W.: Acute dysentery associated with two types of B. dysenteriae. Univ. of Penn. Med. Bull., 1903–1904, xvi, 177.

HASTINGS, DUVAL AND SCHORER: Studies from The Rockefeller Inst. for Med. Res., 1904, ii.

(203) STITT, E. R.: Practical bacteriology, blood work and animal parasitology. Philadelphia, 5th ed., 1918, p. 187.

(204) MACADAM, WM.:† An account of an infection in mesopotamia due to a bacillus of the Gaertner-Paratyphoid group. Jour. R. A. M. C., 1919, xxxiii, 140, and Lancet, London, 1920, ii, 189.

MACKIE, F. P., AND BOWEN, G. J.: Lancet, London, 1920, ii, 154.

KENNEDY, J. A.: Inagglutinable B. paratyphosus C in India. Jour. R. A. M. C., 1919, xxxiii, 190.

HIRSCHFELD, L.: New germ of paratyphoid. Lancet, February 22, 1919.

(205) LEWY, F. H.,* AND SCHIFF, F.:* A third form of paratyphoid. Berl. Klin. Woch., Berlin, 1919, lvi, 1059.

DUDGEON, L. S., AND URQUHART, A. L.:* Paratyphoid "C" bacillus as a cause of paratyphoid fever. Lancet, London, 1920, ii, 15.

JORDAN: Differentiation of paratyphoid enteriditis group. Jour. Inf. Dis., xxii, 252 and 511.

PFEILER, W., AND ENGELHARDT, F.: Zeit. f. Imm. u. Exp. Ther., 1919, 1. Teil originale, Heft 6, 434.

SEIFFERT: Ztschr. f. Hyg. u. Infectionskrankh., 1909, lxiii, 273.

DEAN, A.:* Isolation of organism resembling paratyphoid group. Med. Jour. of Australia, Sidney, 1920, i, 27.

MARUTA, M.:* Bull. of Naval Med. Assn. of Japan, Tokyo, 1918, No. 20, p. 1.

BROUGHTON-ALCOCK* AND LAGANE:* Atypical strain of B. paratyphosus. Lancet, London, 1919, ii, 1023.

KRUMWIEDE, C., JR., PRATT, J. S., AND KOHN, L. A.: Studies on the paratyphoid enteriditis group: I. Xylose fermentation for the differentiation of B. paraphyosus A from other members of the paratyphosus enteriditis group. Jour. Med. Research, Boston, 1916, xxxiv, 355; II. Observations on the reaction in litmus milk as a method of biological differentiation, ibid., 1916–1917, xxxv, 55; III. Some cultural characteristics and their relation to host-origin. Ibid., 357.

SCHITTENHELM, A.:§ Infections with B. enteritidis, Breslau. Münch. Med. Woch., 1920, lxvii, 1309–11.

(206) MORSE, M. E.,* AND TRYON, G.:* Epidemic of dysentery at Boston State Hospital due to member of paratyphoid-enteriditis group. Boston Med. and Surg. Jour., 1917, clxxvii, 255.

TRYON, G.:* Leukocytic reaction in paratyphoid, dysentery and following vaccine inoculation. Ibid., 1920, clxxxiii, 643.

(207) FLETCHER: Several anomalous organisms of the Salmonella group in stools of dysentery and enteric convalescents. Jour. R. A. M. C., 1918, xxx, 57.

ZONDEK, S. G.:* Ueber kombiniertes Auftreten von Infektions-krankheiten. 1. Typhus and Ruhr, 2. Fleckfieber u. Ruckfallfieber. Berl. klin. Woch., 1919, xl, 945–948.

Digitized by Google

(208) PERRY, H. M., AND TIDY, H. L.: Med. Res. Com. Spec. Repts. London, 1919, No. 24.
(209) TENBROECK, C.: A note on the invasion of the bodies of infants by B. dysenteriae. Boston Med. and Surg. Jour., 1915, clxxiii, 284.
(210) SCHLOSS, O. M.: Personal communication.
(211) KENDALL, A. L.: The isolation of B. dysenteriae (Shigae) from the blood of an infant. Boston Med. and Surg. Jour., 1913, clxix, 741.
ROSENTHAL: B. dysenteriae from the heart' sblood at autopsy (adult). Deutsch. Med. Woch., 1903, 97.
BOYD, J. S. K.: Case in which B. dysenteriae (Flexner Y) was recovered from the blood stream during life. Lancet, London, 1919, ii, 482.
DARLING AND BATES: The isolation of B. dysenteriae (Shiga) from the blood stream (adult). Am. Jour. Med. Sc., 1912, cxliii, 36.
GILDEMEISTER AND BERTHLEIN: B. dysenteriae (Flexner) in the blood stream of an infant. Deutsche. Med. Woch., 1914, 478.
DE SAUTELLE, W. T.: A case of B. dysenteriae septicemia. Jour. Amer. Med. Assn., Chicago, 1914, lxiii, 1853.
(212) MARKWALD: Ein Fall von epidem. dysenterie beim Fötus. Münch. Med. Woch., 1901, No. 48, p. 1920.
MARKWALD: Deutsche. Med. Woch., 1901.
(213) CAUSSADE, G.,† AND MARBAIS, S.:† Septicemie à bacille de Shiga et absence de ce bacille dans les selles. Bull. et mém. soc. méd. d. hôp. de Paris, 1919, 3. ser., xliii, 145–151.
(214) MÜHLMANN: Arch. f. Hyg., 1909, lxix, 401.
BRÜCKNER: Deutsch. Med. Woch., 1910, p. 2047.
(215) DUVAL, C. W., AND BASSETT, V. H.: The etiology of the summer diarrheas of infants; a preliminary report. Am. Med., Philadelphia, 1902, iv, 417, and Stud. Rockefeller Inst. M. Research, New York, 1904, i.
(216) WEBSTER, R.:* Blood culture in summer diarrhoea. Med. Jour. of Australia, Sydney, 1919, i, 460.
(217) CREIGHTON, C., WAGNER, C. E., AND DAVISON, W. C.:*†§ The isolation of B. dysenteriae (Flexner) from the urine of an infant with dysentery. Bull. Johns Hopkins Hospital, Baltimore, 1921, xxxiii, 50–51.
(218) FRAENKEL, ERNST:† Researches on pseudodysentery (Y dysentery). Deutsch. Med. Woch., 1915, xli, 1182.
(219) HILGERS, W. E.:† Pseudodysentery bacilli as a cause of cysto-pyelitis. Centr. f. Bakt., 1919, lxxxiii, abt. 1, orig. 414.
FOERSTER, ALFONS:† A case of cysto-pyelitis caused by dysentery bacilli (type Flexner). Münch. Med. Woch., 1918, lxv, 205.
(220) BAYNE-JONES, S.: Personal communication.
(221) SPENCE, R. C., AND MCLEAN, S.: A method of obtaining direct cultures from intestinal ulcers in infants and young children. Jour. Am. Med. Assn., 1920, lxxv, 742.
MANSON-BAHR, P., AND GREGG, A. L.: Diagnosis of dysentery by sigmoidoscope, Lancet, London, 1921, i, 1121–1125 and Tr. Roy. Soc. Trop. Med. and Hyg., London, 1920–1921, xiv, 88–92.
(222) WHITMORE, E. R., AND GRAHAM, D.: Bacillary dysentery. Nelson Loose Leaf Medicine, New York and London, 1920, ii, 160–176.

Digitized by Google

WHITMORE, E. R.: The dysentery bacillus with a bacteriological study of an epidemic of bacillary dysentery in the Philippines. Philippine Jour. of Science, (Sec. B, Med. Sc.), 1911, vi, 215.

(223) VIRCHOW: Virchow's Archiv., 1863, v, 348.

(224) ROKITANSKY: Pathological Anatomy, ii, 265.

(225) CHRISTIANSEN, M.:† Bacillary dysentery in monkeys. Meddelelser fra d. Kgl. Vet. og Landbohojskoles Serumlab. Kjobenh, 1918, lv.

(226) LÜDKE: On the dysentery toxin. Jour. of Path. and Bact., 1905, x, 328.

LÜDKE: Ueber die Gewinnung von dysenterietoxin. Berl. klin. Woch., 1906, xliii, 3 and 54.

(227) KIKUCHI: Untersuchung über die Shiga-Kruseschen Dysenterie bazillus. Archiv. f. Hyg., 1905, lii, 378.

(228) DOPTER, C.: Les Dysenteries, Paris, 1909, 75 ff.

DOPTER, C.: Ann. Inst. Past., 1905, xix, 353–365.

(229) ELLINGER, A., AND ADLER, L.:† Die Wirkung von Ruhrgift auf Kreislauf. Arch. f. exper. Path. u. Pharmakol., 1919, lxxxv, 95.

(230) BESREDKA, A.:† On the mechanism of dysenteric infection, antidysenteric vaccination per os, and the nature of antidysenteric immunity. Ann. de l'Inst. Pasteur, Paris, 1919, xxxiii, 301.

(231) DODGE: Jour. Trop. Med., March 1, 1905.

(232) MAXCY, K. F.: Transmission of infection through the eye. Jour. Am. Med. Assn., 1919, lxxii, 636.

CORPER, H. J., AND ENRIGHT, J. J.: The eye as a portal of infection in respiratory diseases. Jour. Am. Med. Assn., 1920, lxxiv, 521.

(233) BORDET, J.,† AND CIUCA, M.:† Exsudats leucocytaires et autolyse microbienne transmissible. Compt. rend. Soc. de biol., Paris, 1920, lxxxiii, 1293–1295.

BORDET, J., AND CIUCA, M.:† Le bacteriophage de d'Herelle, sa production et son interpretation. Ibid., 1296–1298.

BORDET, J., AND CIUCA, M.: Determinisme de l'autolyse microbienne transmissible. Ibid., 1921, lxxxiv, 276–278.

BORDET, J., AND CIUCA, M.: Specificité de l'autolyse microbienne transmissible. Ibid., 278–279.

BORDET, J., AND CIUCA, M.: Autolyse microbienne et serum antilytique. Ibid., 280–282.

BORDET, J., AND CIUCA, M.:§ Rémarques sur l'historique des recherches concernant la lyse microbienne transmissible. Ibid., 745–746.

BORDET, J., AND CIUCA, M.:§ Evolution des cultures de coli lysogene. Ibid., 747–748.

BORDET, J., AND CIUCA, M.:§ Guerison et retour a l'état primitive, par le serum antilytique, du coli lysogene. Ibid., 748–750.

BORDET, J.: Hemolytic exudates and transmissible bacterial autolysis. Johns Hopkins Bulletin, Baltimore, 1921, xxxii, 302–304.

(234) SLOCKER, S.:* Gallstones and abscess in liver without jaundice. Siglio Medico, Madrid, 1920, lxvii, 121.

MEBANE, T. S.: Diagnosis and treatment of amebic abscess of the liver. Jour. Amer. Med. Assn., 1920, lxxv, 1566.

(235) CARLES, J.:* Paratyphoid fevers and dysentery. Progrès Méd., Paris, 1917, xxxii, 45.

Digitized by Google

(236) LEMOINE: Quoted by SHIGA, K.: Mod. Med. 2. ed (Osler and McCrea), Philadelphia and New York, 1913, i, 773.
(237) IWASKI: Quoted by SHIGA, K.: Mod. Med. 2. ed. (Osler and McCrea), Philadelphia and New York, 1913, i, 777.
(238) SONNE, C.: Zeitschr. f. Klin. Med., 1914, lxxxi, 73.
(239) DOBELL, C., GETTINGS, H. S., JEPPS, M. W., STEPHENS, J. B.: Study of 1300 convalescent dysentery cases in English Hospitals. Med. Res. Com., Spec Rep., Series London, 1918, No. 15.
ARKWRIGHT, J. A.,* YORK, W.,* PRIESTLEY, O. H.,* AND GILMORE, W.:* Examination of fifty dysentery convalescents for carriers. Brit. Med. Jour., London, 1916, i.
SCHORER, E. H.: Typhoid, paratyphoid and dysentery carriers among returning overseas troops. Jour. Amer. Med. Assn., Chicago, 1919, lxxiii, 763.
(240) SCHLESINGER, H.:* Mild dysenteric polyneuritis following dysentery. Med. Klinik, Berlin, 1915, xi, 381.
(241) DUVAL, C. W., AND LEMANN, I. I.: Acute bacillary dysentery. Forscheimer's Therapeusis of Internal Diseases, New York and London, 3rd ed. 1917, Appleton & Co., ii, p. 306.
(242) BRODRIFF: Ind. Med. Gaz., 1907, p. 172.
(243) ROSENTHAL, G.:† Notes sur une epidemie de dysenterie bacillaire. Paris Méd., 1919, ii, 328.
STETTNER, E.: Gelenkrheumetismus und Ruhr. Münch. Med. Woch., 1917, lxiv, 854.
(244) MANSON-BAHR, P.: Commoner complications of bacillary dysentery in military practice. Brit. Med. Jour., London, 1920, i, 791–792.
(245) MARTIN, J. F.,*† AND DEBARD, A.:*† Dysenterie et oedèmes. Lyon Méd., 1919, cxxviii, 225–230 and 281–286.
(246) ISENSCHMID, R.:* Influence of diet on the water content of the body. Schweiz. Med. Woch., Basel, 1920, l, 381.
(247) RUMPEL† AND KNACK:† Abstracted in Med. Suppl., London, 1918, i, 97a.
KESTNER, O.,† AND RENNEN, C.:† Kriegsoedeme und Ruhr. Arch. f. Schiffs- u. Tropen-Hyg., 1919, xxiii, 148.
(248) OBERNDORFER:† Med. Suppl., London, 1919, ii, 29b.
(249) THÉBAUT: These de Paris, 1899; also NENNINGER, Schiffs- und Tropen-Hyg. November, 1903.
GUNSON, E. B.:* Cardiac symptoms following dysentery in soldiers. Lancet, London, 1916, ii, 146.
(250) LESIEUR: Enterites simples et dysenteries. Paris Médical, 1917, No. 4.
(251) OSLER, WILLIAM: The Principles and Practice of Medicine, 8th ed., New York and London, 1918, Appleton & Co.
(252) VIVES, J.† Appendicites et pseudo-appendicites dysenteriques. Theses de Paris, 1918–1919, cclxvii.
LE ROY DES BARRES: Appendicite et dysenterie amibienne. Bull. et mém. Soc. de Chir. de Paris, 1912, xxxviii, 268.
LENTZ, W.: Blind-darmentzündung und Dysenteria-Amöben. Arch. f. Schiffs- u. Tropen-Hyg., 1910, xiv, 952.
HOGAN, E. P.: Appendicitis caused by endameba histolytica. Jour. Amer. Med. Assn., 1920, lxxiv, 727.

Digitized by Google

(253) Nolf, P.: Vaccinotherapy in acute and chronic bacillary dysentery. Jour. Amer. Med. Assn., 1919, lxxiii, 1177–1179.

(254) Cordier, V.:* Tetany from hemorrhage in parathyroids. Ann. de Méd., Paris, 1920, vii, 346.

(255) Herschmann, H.:* Meningitis following bacillary dysentery. Wien klin. Woch., Vienna, 1920, xxxiii, 83.

(256) Miloslavich, E.:† Uber post dysenterische Mastdarmerkrankungen. Med. Klin., 1919, xv, 636.

(257) Cantlie: Manual of Tropical Medicine, 3. ed. (Castellani, A., and Chalmers, A. J.), London and New York, 1919, p. 1852.

(258) Mole, R. H.:* Unusual pathological conditions of the intestines. China Med. Jour., Shanghai, 1920, xxxiv, 115.

(259) Brüning:† Ein Fall von Darmverschluss nach Ruhr. Münch. Med. Woch., 1919, lxvi, 213–214.

(260) Loeper, M.:† La coelialgie durable des dysenteries. Progres. Méd., 1919, 49–52.

Carles, J.,* and Froussard:* The gastrointestinal sequels of dysentery and paratyphoid. Arch. de Mal. de l' app.Dig. etc., Paris, 1916, ix, 136.

Albu, A.:† Die Identität der Colitis ulcerosa und postdysenterica. Med. Klin., 1920, xvi, 1003–1005.

(261) Alexander, A.:† Die postdysenterischen Magen- und Darmer-krankungen und ihre Behandlung. Ztschr. f. phys. u. diätet. therap., 1919, xxiii, 41–49.

(262) Galambos: Quoted by Whitmore, E. R., and Graham, D.: Bacillary dysentery. Nelson Loose Leaf Medicine, New York and London, 1920, ii, p. 173.

v. Lippmann, R.: Combination of dysentery and typhoid resulting in fatal marasmus. Med. Klinik, 1920, xvi, 604–607.

(263) Findlay, G. M.:* Differential diagnosis of amebic and bacillary dysentery from blood. Lancet, London, 1919, ii, 135.

(264) Strauss, H.:* Etiology of dysenteriform affections. Archiv. f. Verdauungs Krankheiten, Berlin, 1915, xxi, No. 1.

(265) Low, G. C.:*† Some unusual forms of dysentery. Brit. Med. Jour., London, 1920, i, 255–256.

(266) de Medeiros, C.:* Dysenteroid syndrome with inherited syphilis. Brazil Medico Rio de Janeiro, 1920, xxxiv, 189.

(267) Devic, M.,* and Bouchut, M. L.:* Symptoms of dysentery with uterine disease. Arch. des Maladies de l'App. Digestif, Paris, 1919, x, 346.

(268) Levy, R. L., and Rowntree, L. G.: On the toxicity of various commercial preparations of emetin hydrochloride. Arch. Int. Med., Chicago, 1916, xvii, 420.

Dale, H. H.: A preliminary note on chronic poisoning by emetine. Brit. Med. Jour., London, 1915, ii, 895.

Dopter, C.:† Note sur la dose limite de l'émétine. Bull. Soc. de therap., 1919, 4. s., xxiv, 130–131.

Mattei, C.:* Cumulative effect of emetin. Bull. de la Soc. Méd. des Hôp., Paris, 1920, xliv, 531.

Savignac, R.,† and Alivisatos, A.:† Un cas d'intolerance à l'émétine, etc. Bull. et Mém. Soc. Méd. d. Hôp. de Par., 1919, 3e sér., xliii, 214–216.

(269) Kartulis: Quoted by Shiga, K.: Mod. Med. 2. ed. (Osler and McCrea), Philadelphia and New York, 1913, i, p. 777.

(270) Jacki: Outbreak of dysentery in infants. Monatsch. f. Kinderh., Berlin, 1920, xviii, 340–351.

Digitized by Google

(271) WOMACK, N. C.: Ileocolitis (Proc. South. Med. Assn., November 10–13, 1919). Jour. Amer. Med. Assn., Chicago, 1919, lxxiii, 1797.
WOMACK, N. C.: Calomel in ileocolitis. So. Med. Jour., Birmingham, Ala., 1920, xiii, 406.
(272) HOWLAND, J., AND MARRIOTT, W. McK.: Acidosis. Penn. Med. Jour., Athens, 1917–1918, xxi, 429.
(273) AMBERG, S.: Contribution to the study of amebic dysentery in children. Johns Hopkins Hosp. Bull., 1901, xii, 355.
DE BUYS, L. R.: Amebic dysentery in children. Jour. Amer. Med. Assn., Chicago, 1914, lxiii, 1806.
LESNÉ,† AND RAMOND, L.:† Un cas de dysenterie amibienne autochthone chez un enfant. Bull. Soc. de pediat., 1919, xvi, 106.
(274) Correspondence. Dysentery among U. S. Troops at Vera Cruz. Jour. Amer. Med. Assn., Chicago, 1914, lxiii, 256.
MITCHELL, S. WEIR: The Principles and Practice of Medicine 8. ed. (Osler, W.). New York and London, 1918, p. 5.
(275) PANAYOTATOU, A.:* Acute amebic heptatitis. Bull. de la Soc. méd. des Hôp., Paris, 1920, xliv, 1217.
(276) FORD: Jour. of Trop. Med., July 15, 1904.
(277) HOLLAND, C. T.:* Roentgenography in dysentery and other cases. Ann. of Trop. Med. and Parasit., Liverpool, 1917, x, 357–360.
(278) BROWN, L., AND SAMPSON, H. L.:† The early roentgen diagnosis of ulcerative tuberculous colitis. Am. Jour. Roentgenol., 1919, vi, 625.
(279) MARFAN, A. B.:* Restricting an infant to water. Le Nourrisson, Paris, 1919, vii, 257.
(280) GÖPPERT, F.:* Zur Behandlung der Ruhr. Berl. klin. Woch., 1914, li, 1697.
LOEPER, M.:* The loss of nourishment in dysentery. Arch. des Maladies de l'App. Digestif, Paris, 1919, x, 153.
(281) BLACKFAN, K. D., AND MAXCY, K. F.: The intraperitoneal injection of saline solution. Am. Jour. Dis. Child., 1918, xv, 19.
AIKMAN, J.: Methods of introducing saline and other fluids to infants and children. Jour. Amer. Med. Assn., 1920, lxxiv, 244.
MCLEAN, S.,* AND LANG, C. A.:* Fluid injections in dehydrated infants. Am. Jour. Dis. Child., Chicago, 1920, xix, 359.
(282) COYNE AND AUCHÉ: Practical Bacteriology, Microbiology and Serum Therapy. Eng. trans. of 5. ed. (French) (Besson, A., and Hutchens, H. J.), London and New York, 1913, p. 362.
(283) FLEXNER, S., AND AMOSS, H. L.: The rapid production of antidysenteric serum. Jour. Exper. Med., 1915, xxi, 515.
(284) FIKUHARA, Y.:*† New method of testing antitoxic dysentery serum. Jour. of Immun., Baltimore, 1919, iv, 299.
SORDELLI, A.: Emploi de petits oiseaux pour mesurer l'activite de la toxine dysenterique et titrer le serum antidysenterique. Compt. rend. Soc. de biol., Paris, 1920, lxxxiii, 1245–1246.
(285) JOSEPHS, H. W., AND DAVISON, W. C.: Sero-therapy of bacillary dysentery in children. Jour. Amer. Med. Assn., Chicago, 1921, lxxvii, 1863–4.
(286) GÖRNER: Die Therapie der Bazillen-ruhr. Munch. Med. Woch., 1919, lxvi, 427.
GROBER, J. A.:* Zur Klinik der Bazillen-Ruhr. Deutsche. Med. Woch., Berlin, 1914, xl, No. 40.

Digitized by Google

MATHIÉU, A.:* Treatment of acute and subacute dysenteric colitis. Presse Médicale, Paris, 1914, xxii, 645.

THOMSON, D., AND MACKIE, T. J.: Jour. R. A. M. C., 1917, xxviii, 403.

CECIKAS, J.:* Masked dysentery. Grèce Médicale, Athens, 1917, xix, 13.

RODENACKER:* Dysentery. Deutsche Med. Woch., 1916, xlii, 1548.

DUFOURT, P.,* AND DEVIC, A.:* Acute bacillary dysentery. Lyon Médical, 1917, cxxvi, 541.

JACOB, L.: Ueber eigenartige Rezidive bei Bazillenruhr. Münch. Med. Woch., 1917, lxiv, 125–127.

JACOB, L.: Ueber die Behandlung der Ruhr mit polyvalenten Serum. Ibid., 1918, lxv, 640–642.

(287) FISHER, J. B.:* Treatment of acute bacillary dysentery. Brit. Med. Jour., London, 1917, i, 43.

FINLAYSON, G. A.:* Treatment of acute bacillary dysentery. Ibid., 47.

CRICHLOW, N.:* Treatment of acute bacillary dysentery. Tropical Med. and Hygiene, London, 1921, xxiv, 204.

(288) LANTIN, T.:* Various methods of serum application in bacillary dysentery. Philippine Jour. Science, Manila, 1918, xiii, 261.

(289) SMITH, L. W., Personal communication.

(290) NELLI, LUIGI:*† Serum therapy in dysentery. Gaz. degli Ospedali e delle cliniche, 1919, Anno XL, 220–222.

(291) DOBRASHIAN, G. M.: An investigation into the results from the treatment of bacillary dysentery by serum and by salines respectively (Malta). Jour. R. A. M. C., xxx, 441.

(292) KORENTCHEWSKY: Practical Bacteriology, Microbiology and Serum Therapy. Eng. trans. of 5. ed. (French), (Besson, H., and Hutchens, H. J.), London and New York, 1913, p. 562.

(293) SCHULTZ-BASCHO, P.:‡ Clinical notes on bacillary dysentery during childhood. Archives f. Kinderh., 1921, lxix, H. 3–4, 269.

KRAMER, J. G.: Personal communication.

(294) WATESON, GEORGE, (HAKLUYT RICHARDS): The cures of the diseases in Forraine, attempts of the English Nation, 1598, publ. by the Clarendon Press, Oxford.

(295) GHIGOFF, B.:* Sodium sulphate in dysentery and cholera. Wien. klin. Woch., Vienna, 1915, xxviii, No. 23.

(296) PEISER, H.:* Disturbance in internal secretion in dysentery. Deutsche Med. Woch., 1915, xli, No. 3.

(297) v. GRÖER, F.:* Epinephrine in treatment of bacillary dysentery. Münch. Med. Woch., Munich, 1915, lxii, No. 14.

(298) BASTEDO, W. A.: The treatment of mucous colitis. Jour. Am. Med. Assn., 1920, lxxiv, 240.

(299) WOODS, (Philadelphia), STEPHEN MACKENZIE, (1882), HEWES, (Boston): Dysenteries, their differentiation and treatment, (Rogers, L.). Oxford University Press, 1913, p. 292.

(300) HARPER, W. W.: Treatment of entero-colitis in infancy. (Trans. Southern Med. Assn.) Jour. Amer. Med. Assn., 1919, lxxiii, 1899.

(301) BERTHA: Quoted by SHIGA, K.: Mod. Med. 2. ed. (Osler and McCrea), Philadelphia and New York, 1913, i, p. 780.

(302) LUTSCH, W.:* Salicylic enemata in dysentery. Munch. Med. Woch., 1914, lxi, No. 9.

Digitized by Google

(303) Escomel, E.:* Bacillary dysentery in Peru. Cronica Medica, Lima, Peru, 1919, xxxvi, 339.

(304) Schiff, E.:† Behandlung der Dysenterie mit Formalininjektionen. Wien klin. Woch., 1919, xxxii, 1005–1007.

(305) Lockhart-Mummery, P.:* Operative treatment of ulcerative colitis. Brit. Med. Jour., London, 1920, i, 497.

Niklas, F.:§ Appendicostomy in chronic dysentery. Deutsche Med. Woch., Berlin, 1920, xlvi, 1026–1028.

Thierry, W.: Beitrag zur chirurgischen Behandlung der Ruhr. Beihefte z. Arch. f. Schiffs- u. Tropenhyg., Leipz, 1919, xxiii, 128–131.

Cotte, G.:* Surgical treatment of acute rebellious dysenteries. Médicine, Paris, 1919, i, 22.

Cotte, G.: †De l'appendicostomie suivie de lavages au nitrate d'argent dans le traitment des dysenteries aiguës rebelles. Bull. et mém. Soc. Méd. des Hôp. de Par., 1919, 3 s., xliii, 119–122.

(306) Cooke: Dysenteries, their differentiation and treatment (Rogers, L.). Oxford Univ. Press, 1913, p. 292.

(307) Bryson, J. G.:* Clinical aspects of bacillary dysentery in Texas. Texas State Jour. of Med., Fort Worth, 1915, xi, No. 1.

(308) Rogers, L.:* Bactericidal action of organic silver salts and other antiseptics on B. dysenteriae. Indian Jour. Med. Res., Calcutta, 1913, i, No. 2.

Rogers, L.: The rational treatment of chronic bacillary dysentery and the advantages of silver gelatose. Brit. Med. Jour., London, 1913, ii, 1198.

(309) Nolf, P.: Injections of peptone in the treatment of typhoid fever and other infections. Archiv. Méd. Belges, February, 1917, 70th year, No. 2.

Nolf, P.: Intravenous injections of peptone in septicemia of traumatic origin and in severe infections. Ambulance de l'Ocean, La Panne, July, 1917, Fasiculi 1.

Nolf, P.: Proteosotherapy by the intravenous method. Jour. Amer. Med. Assn., 1919, lxxiii, 1579.

(310) Borrello, F. P.:* Vaccine therapy of dysentery in children. Pediatria, Naples, 1919, xxvii, 550.

Korlsch, R.,*†§ and Gross, A.:*†§ Vaccine treatment of colitis ulcerosa. Deutsche Med. Woch., Berlin, 1920, xlvi, 735–736.

Forster, W. H. C., (India); Gillet, (Bengal): Dysenteries, their differentiation and treatment, (Rogers, L.). Oxford Univ. Press, 1913, p. 293.

Damade, R.:* Acute dysenteric syndromes. Jour. de Méd. de Bordeaux, 1920, xci, 473.

Damade, R.:§ A study of an epidemic of bacillary dysentery, Thesis. Univ. Bordeaux, 1919, and Press. Méd., 1919, xxvii, 552.

(311) Castellani, A., and Greig: Manual of Tropical Medicine, 3. ed. (Castellani and Chalmers), London, 1919, p. 1858.

(312) Rogers, L.: Sensitized Shiga and Flexner vaccines in the treatment of chronic bacillary dysentery. Brit. Med. Jour., London, 1916, i, 7.

Godson, (East Bengal): Dysenteries, their differentiation and treatment (Rogers, L.). Oxford Univ. Press, 1913, p. 293.

Karström, W.:* Vaccine therapy in epidemic of paradysentery. Upsala Läkareforening Förhandlinger, 1921, xxxvi, 57–82.

Digitized by Google

(313) WHITTINGTON, T. H.: The use of stock vaccines in infection by the bacillus typhosus with an analysis of 230 cases. Lancet, London, 1916, i, 759.

(314) STUMPF, J.:† Bolus alba in diarrhoea, dysentery and cholera. Münch. Med. Woch., 1914, lxi, No. 40.

WOLF-EISNER:* Kaolin-charcoal treatment of diarrheic processes. Therapie der Gegenwart, Berlin, 1915, lvi, No. 3.

(315) HIRSCH, C.:* Ueber Ruhr und ihre Behandlung im Felde. Deutsche Med. Woch., Berlin, 1915, xli, No. 40.

(316) WIESE, O:* Zur Behandlung der Bazillenruhr. Deutsch. Med. Woch., 1916, xlii, 1443.

(317) OSLER, WILLIAM: The Principles and Practice of Medicine, 8. ed. New York and London, 1918, Appleton & Co., p. 5.

(318) GRAHAM-SMITH, G. S.: Bacilli isolated from flies in normal surroundings and in surroundings associated with epidemic diarrhoea. Loc. Gov. Board Reports, 1911–1912, xli, Appendix B., No. 4, p. 304.

(319) MANSON-BAHR, P.: Report of the London School of Tropical Medicine on investigations on dysentery in Fiji during the year 1910. London, 1912, Witherby & Co., 77, p. 80. Suppl. no. 2, J. Lond. School Trop. M.

COX, G. L., LEWIS, F. C., AND GLYNN, E. E.: The number and varieties of bacteria carried by the common house fly in sanitary and unsanitary city areas. Jour. Hyg., Cambridge, 1912, xii, 290–319.

WOODCOCK, H. M.: Note on the relative proportions of amoebic and bacillary dysentery among the troops of the Egyptian Expeditionary Force during the season of 1917; together with some remarks on the question of cyto-diagnosis. Jour. R. A. M. C., London, 1920, xxxiv, 121–130.

(320) DUDGEON, L.:† Bacillary dysentery. Brit. Med. Jour., London, 1919, i, 448–451.

(321) VINCENT: Quoted by DOPTER, C.: Les Dysenteries, Paris, 1909.

(322) BUCHANAN, G. E.:* Study of an outbreak of bacillary dysentery. Lancet, London, 1918, ii, 166–168.

STOOKEY, G. V.:*§ An epidemic of water-borne dysentery. Jour. Infec. Dis., Chicago, 1919, xxv, 331–334.

(Current comment.) Another water supply "accident." Jour. Amer. Med. Assn., Chicago, 1920, lxxiv, 606–607.

(323) READ: Mém. de Méd., Milit., 1871.

(324) COPPINGER: Hygiene and Diseases of Warm Climates (Davidson, A.). Edinburgh, 1893.

(325) KNOX, J. H. M., JR., AND POWERS, G. F.: Report of the babies milk fund association of Baltimore. Transactions of the Am. Child Hygiene Assn., Albany, New York, x, 275–279, and Jour. Amer. Med. Assn., Chicago, 1922, lxxviii, 707–710.

(326) STITT, E. K.: The diagnosis and treatment of tropical diseases. 2. ed., Philadelphia, 1917, P. Blakiston's Son & Co., p. 120.

(327) SINNHUBER, F.:* Bekampfung der Kriegsseuchen durch Schutzimpfung. Deutsche Med. Woch., 1915, xli, No. 22.

(328) DEAN, H. R.,* AND ADAMSON, R. S.:* Method for preparation of non-toxic dysentery vaccine. Brit. Med. Jour., 1916, i.

HIRSCH, P.:† Attempts at detoxicating dysentery (Shiga) bacilli for the purpose of protective inoculation. Ztschr. f. Hyg. u. Infectionskrankh., 1919, lxxxix, 176.

Digitized by Google

JÖTTEN, K. W.:† On the use of neutralized antiformin solutions of bacteria for the production of high grade agglutinating dysentery sera. Ztschr. f. Immunitätforsch. u. exper. Therap., 1920, xxix, Orig. 267.

PETRUSCHKY, J.:† Erfahrungen über percutane Schutzbehandlung bei Ruhr. Med. Klin., 1919, xv, 864–865.

(329) BUSSON, B.: Immunization against dysentery with toxin-antitoxin mixtures. Wien. Klin. Woch., Vienna, 1915, xxviii, 853.

(330) GIBSON, H. GRAEME: A new method of preparation of a vaccine against bacillary dysentery which abolishes severe local reaction. Also experiments with this vaccine on animals and man. Jour. R. A. M. C., London, 1917, xxviii, 615–657.

GIBSON, H. GRAEME: Results obtained from the use of anti-dysenteric serovaccine in the field, with regard to the reduction of case incidence. J. R. A. M. C., London, 1918, xxx, 476–485.

(331) SACHS, MÜKE:† Beitrag zur Ruhrschutzimpfung mit Dysbakta Boehncke. Med. Klin., Berlin, 1918, xiv, 317.

STEUERNAGEL:† Med. Suppl., London, 1918, i, 216a.

BISCHOFF:† Med. Suppl., London, 1918, i, 341a.

(332) HOFFMANN, W.:†§ Dysentery prophylaxis. Deutsche. Mil. ärztl. Zeitschr., Berlin, 1918, Nos. 13–14, and Schweiz. Med. Woch., 1920, i, 17.

PAETSCH:† Erfahrungen mit dem Boehnckeschen Ruhrimpfstoff Dysbakta. Deutsche Med. Woch., 1919, xlv, 403–404.

SCHEER, KURT AND ABE: Ztschr. für Immunitätsforschung u. Exp. Therapie, October 23, 1919, Teil. I, Heft 6, 377.

(333) LE MOIGNAC AND PINOY: Les vaccins en emulsion dans les corps gras ou lipovaccins. Compt. rendu, Soc. de Biol., Paris, 1916, lxxix, 201.

LE MOIGNAC AND PINOY: Application à l'homme des vaccins en emulsion dans les corps gras (lipo-vaccins). Ibid., 352.

(334) WHITMORE, E. R., AND FENNEL, E. A.: An experimental investigation of lipovaccines. An additional note, with a note on triple dysentery lipo-vaccine. Jour. Amer. Med. Assn., 1918, lxx, 902.

OLITSKY, P. K.:* Experimental study of vaccination against B. dysenteriae. Jour. Exper. Med., Baltimore, 1918, xxxviii, 69.

(335) LOUSTE, A.,* AND GODLEWSKI, H.:* Bacillary dysentery spread by baker. Bull. de la Soc. Méd. des Hôp. Par., 1919, xliii, 1022.

(336) LEVEUF, J.,* AND HEUYER:* Surgical intervention in dysentery. Paris Médical, Paris, 1920, x, 301.

MULLER, P.:† Contribution à l'étude des dysenteries et leur traitement chirurgical. Thèses de Paris, 1918–1919, ccxciv.

CHIARI, O. M.:* Dysentery. Mittheil. a. d. Grenzgebieten d. Med. u. Chir., Jena, 1920, xxxii, 49.

(337) MORGAN, E. A.:* Infectious diarrhoea. Canadian Med. Assn. Jour., Toronto, 1920, x, 527.

(338) LAVERAN: De la phlebite, de la thrombose et des paralysies comme complications de la dysenterie. Arch. de Méd. mil., Paris, 1885.

PUGIBET, J.: Des paralysies dans la dysenterie chronique des pays chaudes. Revue de Médicine, 1888.

BONARDI, E.: Intorno ad un caso di polinevrite dissenterica con reperto anatomopathologico e histologico. Il Morgagni, 1897.

LEYDEN: Traité des Maladies de la Moelle, 1880.

Digitized by Google

(339) Von Jaksch, Weinberg and Singer: Quoted by Whitmore, E. R., and Graham, D.: Bacillary dysentery. Nelson Loose Leaf Medicine, New York and London, 1920, ii, p. 175.

(340) Arkwright, J. A.: Variation in bacteria in relation to agglutination by salts and by specific sera. Proc. of Path. Soc. of Great Britain and Ireland; abs. in Jour. of Path and Bact., Cambridge, England, 1920, xxiii, 358.

Arkwright, J. A.: Jour. of Path. and Bact., Cambridge, England, 1921, xxiv, 36.

(341) Hormini, K.: Ueber die pathogenen Wirkungen der Dysenterietoxine. Centr. f. Bakt., Jena, 1913, lxviii, Orig. 1te Abt., 342–358.

(342) Hannon, R. R.: Personal communication.

(343) Roger and Domaschino: Soc. de Biol., Paris, 1871.

Delioux de Savignac: Union Médicale, 1867.

(344) Brauer-Eppendorf, L.: Die Ruhr, ihr Wesen und ihre Behandlung, Berlin, 1918, p. 15.

(345) Mayer, A.: Berl. Klin. Woch., 1918, 378, abstracted in Central. f. Bakt., Jena, September 14, 1920, 177.

(346) Zlocisti, T.: Klin. Monatsbl. f. Augenheilk., 1918, lxi, 393, abstracted in Central f. Bakt., Jena, September 14, 1920, 177.

(347) Lemann, I. I.:* A case of bacillary dysentery with pseudomembrane in the vagina and oedema of the abdominal wall. Jour. Amer. Med. Assn., Chicago, 1920, lxxv, 1716. Also published in Am. Jour. Trop. Med., Baltimore, 1921, i, 53.

(348) Twort, F. W.:* Researches on dysentery. British Jour. Exp. Path., London, 1920, i. 237–243.

(349) Vincent, H.:* Vaccination against bacillary dysentery with ether vaccine. Jour. of State Med., London, 1921, xxix, 54, and Compt. rend. Soc. de biol., Paris, 1921, lxxxv, 965–967.

(350) Bonnet, E.,* and Sicard, J.:* De la dysenterie epidemique dans la Bible. Bull. Acad. de Méd., 1920, 3rd ser., lxxiv, 166–169.

(351) Spolverini, L. M.:* Vaccine therapy in enteritis in children. Rivista di Clin. Ped., Florence, 1921, xix, 162–169.

(352) Picard, M. S.:* Cocoa in acute ileocolitis in infants. New Orleans Med. and Surg. Jour., New Orleans, 1921, lxxiv, 165–171.

(353) Ohly, A.:* Treatment of sequelae of dysentery. Archiv. f. Verdauungs-Krankheiten, Berlin, 1921, xxvii, 191–217.

(354) Besson, A.,* and De Lavergne:* Infection with Morgan's bacillus. Paris Médical, Paris, 1921, xi, 449.

Rey, J. F.:†§ A fatal case of dysentery in an adult caused by Morgan's bacillus. Practitioner, London, 1920, civ, 466–467.

Dopter, C.:§ Le pouvoir pathogene des bacilles de Morgan et de Castellani. Bull. Acad. de Méd. Par., 1921, lxxxv, 301.

(355) Vallardi, C.:†§ Studi intorno ad una epidemia di dissenteria bacillare . . . . delle forme miste amebo-bacillari. Ann. d'ig., Rome, 1920, xxx, 544–560.

Vallardi, C.:† On mixed amoebic and bacillary dysentery. Atti d. Soc. lomb. di sc. med. e. biol., 1920, ix, 419.

(356) Stokes, A.,†‡ and Bigger, J. W.:†‡ A short account of dysentery in Dublin in the autumn of 1919. Dublin Jour. Med. Sc., 1920, 4th ser., i, 3–8.

(357) Jennicke, E.:† Zur Ruhrepidemie in Thüringen. Deutsch. Med. Woch., Berlin, 1920, xlvi, 1308–1309.

Digitized by Google

(358) PARAF, J.:† Étude experimentale du rôle des mouches dans le propagation de la dysenterie bacillaire. Rev. d'hyg., 1920, xlii, 241–244.

WOLLMAN, E.: Le rôle des mouches dans le transport des germes pathogenes étudié par la methode des élévages aseptiques. Ann. de l'Inst. Past., Paris, 1921, xxxv, 431–449.

AUCHE, A.: Transport des bacilles dysenteriques par les mouches. Compt. rend. Soc. de biol., Paris, 1906, lviii (2), 450–452.

KRONLOWSKI, A.: Zur Frage uber die Typhus- und Dysenterie-verbreitung durch Fliegen. Centr. f. Bakt., Jena, 1913, lxviii, Orig. I. abt., 586–590.

(359) VOGT, H.:† Zur Bedeutung der Ruhr für des Säuglingsalter. Monatsch. f. Kinderheilk., 1919, xv (orig.), 193–198.

(360) GRAHAM, G.:† Arthritis in dysentery. Proc. Roy. Soc. Med., London, 1919, xiii (Sec. of Med.), 23–42.

(361) GLAESSNER, K.:*†§ Pankreasstörungen bei Dysenterie. Wien klin. Woch., 1920, xxxiii, 859–860.

(362) MOORHEAD, T. G.:† Myelitis as a complication of bacillary dysentery. Med. Press & Circ., 1920, ii, 245.

(363) BUTTENWEISER, S.:† Ein Fall von Encephalitis hemmorrhagica bei Dysenterie. München. Med. Woch., 1920, lxvii, 1472.

(364) BOECK, W. C.:* Chilomastix mesnili and method for its culture. Jour. Exp. Med., Baltimore, 1921, xxxiii, 147.

(365) ORNSTEIN:† Bacteriology of Schmitz bacillus. Ztschr. f. Hyg. u. Infekt., 1920, xci, 152–178.

(366) CSERNEL, E.:† Vaccination against dysentery with sensitised vaccines. Ibid., 53–56.

(367) v. WERDT, F.,*‡ AND KOPATSCHEK, F.:*‡ The growth of dysentery bacilli on albumin-free media. Centralbl. f. Bakt., Jena, 1920, i, 95.

(368) LAUBER, L.:‡§ Dysentery epidemic at Mannheim. Centralbl. f. Bakt., Jena, 1920, lxxxiv, I. Abt. Orig. 201–214.

(369) JOB, E.,† AND HIRTZMANN, L.:† Dysenterie bacillaire et paludisme. Bull. et mém. soc. méd. d. Hôp. de Par., 1919, 3e ser., xliii, 714–718.

(370) LEDINGHAM, J. C. G.: Dysentery and enteric disease in Mesopotamia from the laboratory standpoint. Jour. R. A. M. C., London, 1920, xxxiv, 189.

(371) JACOBY, F.: The importance of acidity of dysenteric stools in the bacteriological diagnosis of dysentery. Ztschr. f. Hyg. u. Infekt., 1920, xc, 1.

HESS, R., AND SCHEER, K.: Reaction of infants' stools and its relation to causal agents of dysentery. Arch. f. Kinderh., 1921, lxix, 370–377.

(372) HAUGHWOUT, F. G.,† AND LANTIN, P. T.:† Protozoologic and clinical studies on the treatment of protozool dysentery with benzyl benzoate. Arch. Int. Med., Chicago, 1919, xxiv, 383–397.

(373) SOLIMANO, G.:† Agglutination and disintegrative biochemical activities of B. dysenteriae "Shiga." Pathologica, 1920, xii, 113–124.

(374) SIKL, H. T.:† Bacteriological investigations on pathological-anatomical dysenteric material. Ztschr. f. Hyg. u. Infekt., 1920, xc, 337.

(375) LORENZ, F.:† A milk-borne epidemic of dysentery Y. Ibid., 423.

(376) GRATIA, A.: Studies on the lytic agent of Bordet and Ciuca. Proc. of the Soc. of exper. Biol. and Med., New York, 1921, xviii, 192–193.

GRATIA, A.: Preliminary report on a staphylococcus bacteriophage. Ibid., 217–219.

Digitized by Google

GRATIA, A.:† Studies on the d'Herelle phenomenon. Jour. Exper. Med., Baltimore, 1921, xxxiv, 115.

GRATIA, A.: The Twort-d'Herelle phenomenon, II Lysis and microbic variation. Ibid., 1922, xxxv, 287–302.

GRATIA, A.: Influence de la reaction du milieu sur l'autolyse microbienne transmissible. Compt. rend. Soc. biol., Paris, 1921, lxxxiv, 275–276.

GRATIA, A.:§ De l'adaptation heriditaire du colibacille à l'autolyse microbienne transmissible. Ibid., 750–751.

GRATIA, A.:§ Dissociation d'une souche de colibacille en deux types d'individus de propriétés et de virulence différentes. Ibid., 751–753.

GRATIA, A.:§ De la signification des "colonies de bacteriophage" de d'Herelle. Ibid., 753–754.

GRATIA, A.:§ Sur la specifité du principe lytique. Ibid., 755.

GRATIA, A.:§ L'autolyse transmissable du staphylocoque et l'action coagulante des cultures lysées. Ibid., 1921, lxxxv, 25–26.

GRATIA, A.: Autolyse transmissible et variations microbiennes. Ibid., 251–252.

GRATIA, A.,§ AND JAUMAIN, D.:§ Identité du phenomène de Twort et du phenomène de d'Herelle. Ibid., 880–881.

GRATIA, A.,§ AND JAUMAIN, D.:§ Dualité du principe lytique du colibacille et du staphylocoque. Ibid., 882–884.

(377) BLUMENTHAL, G.:† On the aetiology of bacillary dysentery. Ztschr. f. Hyg. u. Infekt., 1920, xci, 335.

(378) GOLDZIEHER, M.:§ Bacteriological and serological studies on dysentery. Centralbl. f. Bakt., Jena, 1921, lxxii, I. Abt. Orig., 437–439.

(379) SIMON, G.:§ The agglutination of B. paratyphosus B in cases of bacillary dysentery. Berl. klin. Woch., 1919, No. 3; also Schweiz. Med. Woch., 1920, i, 37.

(380) BLACKBURN, C. B.:§ Some experience with dysentery in the Palestine campaign. Med. Jour. Australia, Sydney, 1919, ii, 148–150.

(381) FLEXNER, S.:§ Serum treatment of bacillary dysentery. Jour. Amer. Med. Assn., Chicago, 1921, lxxvi, 108.

(382) STREMPEL, R.:§ Observations on dysentery. Centralbl. f. Bakt., Jena, 1920, lxxxv, I. Abt. Orig., 68–80.

(383) MACLEOD, G.:§ Notes on the epidemiology of bacillary dysentery. Pub. Health, London, 1921, xxxiv, 81–84.

(384) HILGERS, W. E.:§ On the E race (lactose race) of pseudo-dysentery bacilli. Ztschr. f. Immunität u. exper. Ther., Jena, 1920, xxx, I Teil, Orig., 77–94.

(385) LOWENTHAL, W.:§ Investigation to explain the agglutination of dysentery bacilli by the sera of pregnant women. Ibid., 439–467.

(386) London letter: The treatment of dysentery in the army. Jour. Am. Med. Assn., Chicago, 1919, lxxii, 742.

(387) Buenos Aires letter: Epidemics of dysentery at Rioja and Catamarca. Ibid., 56.

(388) BISHOP, F. C.,* AND LAAKE, E. W.:* Dispersion of flies by flight. Jour. Agric. Res., 1921, xxi, 729.

(389) MITA, K.:*† Personal communication and: Dysentery-like diseases (paradysentery, paratyphoid) in children and their causes. Jour. Inf. Dis., Chicago, 1921, xxix, 580.

(390) JOB, E.:* Bacillary dysentery. Arch. de Méd. et Pharm. Militaires, Paris, 1921, lxxiv, 368–408.

Digitized by Google

STAWELL, R. R.: Treatment of bacillary dysentery. Med. Jour. Australia, Sydney, 1921, i, 496–497.

(391) DUMAS, J.:† On the presence of bacteriophage in the healthy intestine, in soil and in water. Compt. rend., Soc. de biol., Paris, 1920, lxxxiii, 1314–1315.

(392) DEBRE, R.,† AND HAGUENAU:† Some peculiarities of the "d'Herelle phenomenon." Ibid., 1348–1349 and 1368.

(393) SALIMBENI† AND (PETTIT, A.):† Sur le bacteriophage de d'Herelle. Ibid., 1545–1548.

SALIMBENI AND (PETTIT, A.): Sur le nature du bacteriophage de d'Herelle. Compt. rend. de l'Acad. des Sc., Paris, 1920, clxxi, 1240–1242.

(394) KUTTNER, A.: Preliminary report on a typhoid bacteriophage. Proc. Soc. Exp. Biol. and Med., New York, 1921, xviii, 158.

KUTTNER, A.: On the influence of tissue enzymes on the bacteriophagic principle. Ibid., 222–225.

(395) DAVISON, W. C.: Observations on the properties and nature of bacteriolysants (d'Herelle's phenomenon, bacteriophage, bacteriolytic agent, etc.). I and II. Jour. Bact., Balto., 1922, vii, 475–490, 491–504

DAVISON, W. C.: Bibliographic Review. Filterable "substance" antagonistic to dysentery and other organisms (d'Herelle's phenomenon, bacteriophage, bacteriolytic agent, bacteriolysant, etc.). Abst. Bact., Balto., 1922, vi, 159–177.

DAVISON, W. C.: The bacteriolysant therapy of bacillary dysentery in children. Am. Jour. Dis. Child., Chicago, 1922, xxiii, 531–34.

(396) MCLEOD, J. W., AND GAVENLOCK, P: Lancet, London, 1921, i, 900.

(397) WOLLSTEIN, M.:† Studies on the phenomenon of d'Herelle with B. dysenteriae. Jour. Exp. Med., Baltimore, 1921, xxxiv, 467–476.

(398) FOGES, A.:† Ueber schwere postdysenterische Rektalveränderungen und deren Behandlung (Lichttherapie). Wien klin. Woch., 1919, xxxii, 1250–1251.

(399) HAUGHWOUT, F. G.:† The differential diagnosis of the dysenteries. Philippine Islands Med. Assn., Jour., 1921, i, 53.

(400) JOHNSON, J. G.: Gangrene of caecum and colon in case of acute dysentery. Canadian Med. Assn., Jour., 1920, x, 564–566.

(401) AVERY, O. T., ET AL: Intradermal test and desensitization in the sero-therapy of lobar pneumonia. The Rockefeller Inst. for Med. Res., 1917, Monograph No. 7, 62–64.

(402) SCHMIDT, A.: Zur Kenntnis der Colitis suppurativa. Grenzgeb. d. Med. u. Chir., Bd. xxviii.

SCHMIDT, A.: Die Schweren entzundlichen Erkrankungen des Dickdarms. Arch. f. Verd. Krankh., Bd. xxii, H. I.

(403) HUGHES, B., AND BANKS, H. S.: Immediate surgical complications of dysentery. Brit. Med. Jour., London, 1920, ii, 934–936.

(404) CRICHLOW, N.: Acute bacillary dysentery. Jour. Trop. Med., 1921, xxiv, 204–206.

(405) EGEN, E., KLEMPERER, P., AND STRISOWER, R.: Zur Klinik und pathogenese der Ruhr (mit besonderer Berucksichtigung der rektoskopischen Befunde), Ztschr. f. exper. Path. u. Therap., 1920, xxi, 182–212.

(406) KIRSCHNER, L., AND SEGALL, I.: Zur Bakteriologie der Ruhrerkrankungen des Jahres 1920 in Wien. Wien. klin. Woch., 1920, xxxiii, 1125–1126.

(407) CZAPLEWSKI: Zur Bakteriologie der Ruhr. Centr. f. Bakt., Jena, 1920–1921, lxxxv, I. Abt., Orig. 105–113.

Digitized by Google

(408) DOLD, H., AND FISCHER, W.: Ein Fall von naturlich erworbener, bacillärer Dysenterie beim Hunde (mit gleichzeitiger Schistosomiasis, Ankylostomiasis und Filiariosis). Ibid., 198–206.

(409) STRASBURGER, J.: Chronic bacillary dysentery and sequels. Deutsch. Med. Woch., 1921, xlvii, 441–443.

BRANDEIS, M.: Die subakuten und chronischen Verdauungstörungen nach Ruhr. Arch. f. Verdauungskr., Berlin, 1920, xxvi, 399–429.

LEUSDEN, J. T.:* Ulcerative Colitis. Neder Tijd. v. gen. Amsterdam, 1921, ii, 2890.

(410) MARCOVICI, E.: Das leukozytäre Blutbild bei Dysenterie; bei chronischem und akutem Darmkatarrh; Colica Mucosa; Darmtuberkulose. Folia Haematol., Leipz., 1920, xxvi, I. Teil, 41–44.

(411) DEW, H. R., AND FAIRLEY, N. H.: Dysenteric infections. M. J. Australia, Sydney, 1921, i, 453–460.

(412) KOHLER, M. D.: Zur Ruhrbehandlung mit antidysten. Med. Klin., Berlin, 1920, xvi, 1138.

(413) PATTERSON, S. W., AND WILLIAMS, F. E.: Epidemic diarrhoea. Med. J. Australia, Sydney, 1921, i, 460–464.

(414) KUNTZE, G.: Dysentery in childhood. Med. Klinik, 1921, xvii, 307–311.

(415) KEERSMAKERS: Small epidemic of dysentery. Arch. Med. Belges, 1921, lxxiv, 1–8.

(416) ZOLLER, H. F., AND CLARK, W. M.: Bacilli, production of volatile fatty acids by bacteria of dysentery group. Jour. General Physiol., 1921, iii, 325–330.

(417) WALZ-GEORGES, M.: Two cases of epidemic dysentery in the newly born. Monatschr. f. Kinderh., 1921, xix, 477–479.

(418) MANSON, J. S., AND MITCHELL, H. A.: Small outbreak of dysentery in a provincial town. Lancet, London, 1921, i, 802.

(419) JAFFE, R. H., AND STERNBERG, H.: Ueber die vakuoläre Nierendegeneration bei chronische Ruhr. Virch. Arch. f. path. Anat., Berlin, 1920, ccxxvii, 313–318.

(420) AUFRECHT, E.:* Morphine in pneumonia and dysentery. Therap. Halbmonatschr., 1920, xxxiv, 412.

(421) LOVE, R. J. M.: Surgical complications of dysentery. Practitioner, 1920, cv, 11–25.

(422) WOLLMANN, E.:† Concerning the note of Bordet and Ciuca (d'Herelle's phenomenon, transmissible microbe autolysis of Bordet and Ciuca and Darwin's theory of pangenesis). Compt. rend. Sòc. de biol., Paris, 1920, lxxxiii, 1478–1479.

WOLLMANN, E.:† On the phenomenon of d'Herelle. Ibid., 1921, lxxxiv, 3–5.

WOLLMANN, E.§ AND GOLDENBERG, L.:§ Le phenomène de d'Herelle et la réaction de fixation. Ibid., 1921, lxxxv, 772–774.

(423) PINOY, P. E.: Rôle des myxobacteries. Ann. de l'Inst. Past., Paris, 1907, xxi, 622–656.

PINOY, P. E.: Sur les myxobacteries. Ibid., 1921, xxxv, 486–495.

(424) ELIAVA, G.,§ AND POZERSKI, E.:§ Sur les characteres nouveaux presentés par le bacille de Shiga ayant resisté à l'action du bacteriophage de d'Herelle. Compt. rend. Soc. de biol., Paris, 1921, lxxxiv, 708–710.

ELIAVA, G., AND POZERSKI, E.: De l'action destructive des sels de quinine sur le bacteriophage de d'Herelle. Ibid., 1921, lxxxv, 139–141.

425) NICOLLE, M.: Action du "Bacillus subtilis" sur divèrses bacteries. Ann. de l'Inst. Past., Paris, 1907, xxi, 613–621.

Digitized by Google

(426) HANKIN, E. H.: Les microbes des rivières de l'Inde. Ibid., 1896, x, 175–176.
HANKIN, E. H.: L'action bactericide des eaux de la Jumna et du Gange. Ibid., 1896, x, 511–523.
(427) GENGOU: Contribution à l'étude des substances bacteriolytiques des leukocytes. Bull. Acad. Roy. de Méd. de Belg., Bruxelles, 1920, 4. s., xxx, 993–999.
GENGOU:† Les substances bacteriolytiques des leucocytes et leurs rapports avec l'alexine. Ann. de l'Inst. Past., Paris, 1921, xxxv, 497–512.
(428) BRUYNOGHE, R.,§ AND MAISIN, J.:§ Au sujet des microbes devenus resistant au principe bacteriophage. Compt. rend. Soc. de biol., Paris, 1921, lxxxiv, 847–848.
BRUYNOGHE, R.:* Au sujet de la guerison des germes devenus resistants au principe bacteriophage. Ibid., 1921, lxxxv, 20–23.
BRUYNOGHE, R.: Au sujet de la nature du principe bacteriophage. Ibid., 258–260.
(429) MAISIN, J.:§ Au sujet de la nature du principe bacteriophage. Ibid., 1921, lxxxiv, 467–468.
MAISIN, J.:§ Adaptation du bacteriophage. Ibid., 468–470.
MAISIN, J.:§ Au sujet du principe bacteriophage et des anticorps. Ibid., 755–756.
(430) BESSON, A.,§ AND DE LAVERGNE:§ Sur le Bacille de Morgan. Ibid., 77–79.
(431) FABRY, P.: Sur l'agglutination des microbes attenués. Ibid., 1921, lxxxv, 237–238.
(432) DE MAGALHAES, A.:§ B. fecalis alkaligenes isolated from blood of an individual with a typhoid-like disease. Ibid., 1921, lxxxiv, 591–592.
(433) HILGERS, W. E.: Vierjährige Erfahrungen uber die Ruhr im Felde bei einen Truppenteil im Westen. Offentliche Gesundheitspflege, 1920, v, 171–180.
(434) STEWART, H. G.: Personal Communications.
(435) ARTHOS AND HUBER: Arch. de Physiol., 1892, iv, 651.
(436) DE KRUIF, P. H.: Dissociation of microbic species I. Jour. Exper. Med., Baltimore, 1921, xxxiii, 773.
DE KRUIF, P. H.: II, III and IV, Proc. Soc. Exp. Biol. and Med., New York, 1921, xix, 34–37, 37–38 and 38–40.
(437) GANTER* AND VAN DER REIS:* The bactericidal function of the small intestine. Deutsch. Arch. klin. Med., Leipzig, 1921, cxxxvii, 348–358.
(438) BAIL, O.:*§ Ueber Shiga Bacteriophagen. Wien. klin. Woch. Vienna, 1921, xxxiv, 555–556.
(439) POORTER, P. DE, AND MAISIN, J.: Contribution à l'étude de la nature du principe bacteriophage. Arch. Internat. de Pharmacodyn. et de Therap., 1921, xxv, 473–484.
(440) TEAGUE, O., AND MORISHIMA, K-I.: The action of B. typhosus on xylose and some of the other less frequently used sugars. Jour. of Inf. Dis., Chicago, 1920, xxvi, 52–76.
(441) ZINGHER, A.,§ AND SOLETSKY, D.:§ Besredka's method of oral immunization of rabbits with ox bile and paratyphoid bacilli. Proc. N. Y. Path. Soc., New York, 1920, xx, 133–141.
(442) THJOTTA, T.,† AND SUNDT, O. T.:† Toxins of Bact. dysenteriae, Group III. Jour. Bact., Baltimore, 1921, vi, 501.
(443) GAIGER, S. H.,§ AND DALLING, T.:§ Bacillary dysentery in lambs. Jour. Comp. Path. and Therap., Edinburgh and London, 1921, xxxiv, 79–105.
(444) MARTINEZ, A. G.:* Leukocyte count in dysentery. Repertio de Med. y. Chir., Bogota, 1921, xxi, 600.
(445) KANAI, S.:*† Dysentery immunization in rabbits by oral and subcutaneous methods. Brit. Jour. Exper. Path., London, 1921, ii, 256.

Digitized by Google

(446) London letter: Fatal use of the Sigmoidoscope. Jour. Amer. Med. Assn., Chicago lxxviii, 829.
(447) KUNDRATITZ, N.:* Ulcerosa cachetica as a complication in bacillary dysentery. Monatschr. f. Kinderh., Berlin, 1921, xxi, 366–373.
(448) KLIGLER, I. J.:* Investigation on soil pollution and the relation of the various types of privies to the spread of intestinal infection. Monographs of the Rockefeller Inst. for Med. Res. New York, 1921, No. 15, pp. 75.
(449) AOKI, K.:† Über die agglutinatorische Einteiling von dysenteriebazillen, Tohoken. Jour. Exper. M., 1921, ii, 142.
(450) SCHMIDT, G.: Centr. Bakt., Jena, 1902, xxxi, 1te abt., orig., 522.
(451) POWERS, G. F.: Personal Communication.
(452) AINLEY, WALKER E. W.:† Studies in bacterial variability, on the occurrence and development of dys-agglutinable, eu-agglutinable and hyper-agglutinable forms of certain bacteria. Proc. Roy. Soc., Ser. B., 1922, xciii, 54.
(453) DE NECKER, J.:§ The inhibitory action of the bacteriophagous principle upon the development of susceptible organisms. Compt. rend. Soc. de biol., Paris, 1921, lxxxv, 742–744.
(454) APPLEMANS, R.:§ The bacteriophage in the body. Ibid., 722–724.
(455) THJOTTA, TH.,§ AND SUNDT, O. F.:§ A small epidemic of dysentery caused by dysentery of Group I (B. shigae). Nord. hyg. Tidsskr., 1921, ii, 1.

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* Abstracts of these references may be found in the Journal of the American Medical Association, (Chicago), 1916–1921. LXVI–LXXVII.

† Abstracts of these references may be found in Medical Science, Abstracts and Reviews, Oxford University Press, 1919–1921. I–V.

‡ Abstracts of these references may be found in the International Medical Digest, (W. F. Prior Co., Hagerstown, Md., publishers), 1920–1921. I–II.

§ Abstracts of these references may be found in Abstracts of Bacteriology, (Baltimore), 1920–1921. IV–V.

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